Case Report

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Familial hepatic rupture in vascular Ehlers–Danlos syndrome in pregnancy with atypical thromboses

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Lesson

This case highlights the importance of genetic testing over fibroblast testing and presents the first published thromboelastometry data in vascular Ehlers–Danlos syndrome.

Keywords

Vascular Ehlers–Danlos syndrome, liver rupture, thromboelastometry, thrombosis

Case report

A 35-year-old woman underwent an elective laparoscopic cholecystectomy while 18 weeks pregnant with her third baby.

She had had three previous pregnancies; the first was complicated by a third-degree tear and blood loss of 1200 mL, the second was an uncomplicated caesarean section, and the last resulted in a miscarriage at 12 weeks. She was otherwise generally well with a body mass index of 38 kg/m^2 and palpitations managed with bisoprolol. She had undergone varicose vein surgery four years previously.

Immediately post-operatively, a large abdominal haemorrhage was noted, and she was transferred to the regional tertiary hepatobiliary centre for specialist management. At relook laparotomy one day after the original operation, a large hepatic subcapsular haematoma was noted, but no clear cause was identified. She underwent peri-hepatic packing for liver lacerations. She suffered a massive haemorrhage and had two brief hypovolaemic cardiac arrests. She received a blood transfusion of more than 30 units, correction of coagulopathy and ongoing supportive care in the intensive care unit.

Following the second cardiac arrest, the demise of the fetus was confirmed, and on the day after the initial operation, she spontaneously miscarried a male fetus, with minimal blood loss.

Six days later, she deteriorated with abdominal sepsis and returned to theatre for removal of the abdominal packs, and no significant bleeding occurred. Her abdomen was left open thereafter.

Over the following few weeks, she made slow but steady improvement. A surgical tracheostomy was inserted to facilitate respiratory weaning. Unfortunately, three weeks after admission, she developed a new acute large subcapsular peri-hepatic haematoma and a mid-thigh haematoma, felt to be spontaneous.

She was found to have multiple proximal deep vein thromboses three weeks after her initial operation, including in the superior vena cava, the right gonadal vein, the right external iliac and femoral veins, and the left common femoral vein. An inferior vena cava filter was fitted, and she was treated with intravenous heparin. Despite extensive coagulopathy testing by the haematology team, no significant abnormalities, including disseminated intravascular coagulopathy, were detected.

Despite the initial improvement, six weeks after her initial operation, she developed new sepsis and further bleeding, this time from the right hepatic artery, in the context of an already ischaemic and infected right liver, requiring escalating multi-organ support, and from which she died.

Concern was raised during the intensive care unit stay about the extent of the bleeding and friable tissues during surgical procedures including tracheostomy. She has had previous varicose vein surgery in 2018 where the friability of the tissue was noted by the vascular surgeon. In addition, the patient was noted to have prominent eyes and a narrow nose with thin vermillion of the lips.

Interestingly, the patient's sister had also developed a large liver haemorrhage five days after a caesarean

section with friable tissues noted at subsequent resuscitative laparotomy around 20 years previously, from which she had died.[1] She was diagnosed with vascular Ehlers–Danlos syndrome. The patient and her mother both had spontaneous features and similar facial features and had a skin biopsy for collagen electrophoresis, which did not show abnormalities. No further investigations were possible at that time and a diagnosis of vascular Ehlers–Danlos syndrome was not confirmed.

During the admission of this patient, contact was made with the national Ehlers–Danlos syndrome service and subsequently blood samples were sent for genetic testing.

Following her death, genetic testing confirmed a diagnosis of vascular Ehlers–Danlos syndrome due to the presence of a pathogenic c.582 + 1G > A splice site variant in the *COL3A1* gene. DNA analysis on a blood sample of the mother identified mosaicism for this *COL3A1* variant. The mother is known to have a mildly dilated thoracic aorta and will have continued cardiovascular surveillance.

Discussion

Written informed consent for details of the case to be published has been obtained from the next of kin.

Vascular Ehlers–Danlos syndrome is an inherited connective tissue disorder, with an estimated prevalence of at least 1:200,000.[2] The 2017 international classification defines vascular Ehlers–Danlos syndrome by the presence of arterial aneurysms, dissection and rupture, rupture of bowel and uterus, and a positive family history of vascular Ehlers–Danlos syndrome. Minor features include thin, translucent skin with venous visibility, acrogeria, extensive bruising, characteristic facies and early onset varicose veins.[3]

The patient in this case was diagnosed at the age of 35 after hepatic rupture, a major complication following cholecystectomy while 18 weeks pregnant. The presentation of this case is common; a review of 630 patients with molecularly confirmed vascular Ehlers–Danlos syndrome showed that 70% of individuals were diagnosed after a major complication. The average age of diagnosis is 30 years.[4]

Importantly, several of the presenting features in this patient are rare, such as hepatic rupture. However, due to generalised tissue fragility, surgery in individuals with vascular Ehlers–Danlos syndrome is usually discouraged unless absolutely necessary due to the increased risk of complications. Despite the large range of clinical complications that can occur in people with vascular Ehlers–Danlos syndrome, the patient and her sister interestingly both had a hepatic rupture which took place in her sister around the time of pregnancy.

A clinical feature of this patient that is only very rarely described in vascular Ehlers–Danlos syndrome was the formation of extensive multiple thromboses. Only two previous case reports have been identified; in one, multiple arterial and venous thrombi were found[5]; in a further report, a 24-year-old female with vascular Ehlers–Danlos syndrome was found to have a deep vein thrombosis; however, this was due to compression by a large posterior tibial artery pseudoaneurysm.[6] In our case, no external compressive or local factors were found to explain the formation of thromboses. It is of note that other connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus are also associated with thrombosis formation.

Due to the combination of excessive bleeding and thrombosis formation, multiple rotational thromboelastometry tests were undertaken on this patient during her admission. The majority of parameters of clot initiation, clot strength and clot lysis of the intrinsic, extrinsic and fibrin contribution pathways were within the normal range (see Table 1). The Extem clot amplitude represents the contribution of fibrin and platelets to clot strength, which was in or above the normal range in over 93% of samples, suggesting that platelet function in these samples was not impaired; this is in contrast to previous work suggesting that over 50% of patients displayed platelet aggregation disorders.[7] To our knowledge, this is the first published thromboelastometry data in a patient with vascular Ehlers–Danlos syndrome.

The risk of pregnancy-related complications is increased in women with vascular Ehlers–Danlos syndrome compared with the general population, with one study finding pregnancy-related deaths occurring in 30 out of 565 deliveries (5.3%).[8] Life-threatening complications occur in 14.5% of deliveries and include arterial dissection/rupture (9.2%), uterine rupture (2.6%), and surgical complications (2.6%).[8] It is strongly advised that women with a diagnosis of vascular Ehlers–Danlos syndrome benefit from being counselled on the risks of pregnancy and, if they were to become pregnant, from being monitored and managed by a specialist team in a tertiary obstetric centre.[2]

Collagen electrophoresis in cultured fibroblasts was performed abroad on this patient and her mother shortly after the death of their family member, approximately 18 years ago. There were no abnormalities seen that were consistent with vascular Ehlers–Danlos syndrome, which may have been falsely reassuring in the initial clinical workup. The patient and her mother would have benefitted from undergoing DNA analysis for vascular Ehlers–Danlos syndrome, which was not routinely available on the National Health Service at that time but is now the gold standard; the mother was subsequently found to be mosaic as the variant. There is a mutation detection rate of approximately 96% for deleterious variants in the *COL3A1* gene.[2] Genetic testing did not take place when the patient presented to our centre either as it was assumed that vascular Ehlers–Danlos syndrome had been excluded in the past.

Table 1. Parameters of clot initiation (clotting time and clot formation time), clot strength (amplitude at 10 minutes and maximum clot firmness) and clot lysis (maximum lysis) of the intrinsic (Intem), extrinsic (Extem) and fibrin contribution pathways (Fibtem). Normal ranges taken from Lang et al.[10]

	Parameter	Normal range	Number of results	Median	Interquartile range	Min, max	Number of results below the normal range, *n* (%)	Number of results above the normal range, *n* (%)
Fibtem	Clotting time (s)	43–69	15	67	58–79	51, 101	0 (0)	5 (33.33)
	Amplitude at 10 minute (mm)	9–24	15	20	12.5–23.5	8, 46	1 (6.67)	3 (20)
	Maximum clot firmness (mm)	9–25	15	22	14.5–25.5	9, 46	0 (0)	4 (26.67)
Extem	Clotting time (s)	42–74	15	69	64–83	51, 113	0 (0)	6 (40)
	Clot formation time (s)	46–148	15	57	48–90.5	37, 255	3 (20)	2 (13.33)
	Amplitude at 10 minutes (mm)	43–65	15	59	52.5–68	31, 78	1 (6.67)	6 (40)
	Maximum clot firmness (mm)	49–71	15	67	63.5–76	42, 83	1 (6.67)	6 (40)
	Maximum lysis (%)	0–18	15	7	5–8	4, 16	0 (0)	0 (0)
Intem	Clotting time (s)	137–246	15	188	174–202.5	151, 249	0 (0)	1 (6.67)
	Clot formation time (s)	40–100	15	67	50.5–105.5	39, 255	1 (6.67)	4 (26.67)
	Amplitude at 10 minutes (mm)	44–68	15	55	50–65.5	30, 73	2 (13.33)	2 (13.33)
	Maximum clot firmness (mm)	52–72	15	64	60.5–73.5	42, 78	1 (6.67)	5 (33.33)
	Maximum lysis (%)	0–12	15	6	5–8	3, 14	0 (0)	2 (13.33)

The diagnosis of vascular Ehlers–Danlos syndrome was eventually discovered on genetic testing, demonstrating the risk of a false negative result with fibroblast testing. In 24 patients with genetic confirmation of their subtype, such as in this case, 7 (29%) had no fibroblast abnormality on normal transmission electron microscopy[9]; in addition, of 177 patients with a clinical diagnosis, 147 (83%) had normal transmission electron microscopy. In view of this, when a diagnosis is suspected on clinical grounds, some authors suggest that molecular genetic testing be the primary diagnostic method.[2]

While this is a single case report which limits its generalisability, it demonstrates the importance of making a diagnosis of vascular Ehlers–Danlos syndrome in an individual. Guidance should be sought from the national Ehlers–Danlos syndrome service regarding undertaking surgical procedures, which should only be performed when absolutely necessary, and when this is the case with extensive precautions due to the presence of generalised tissue fragility.

When a diagnosis of vascular Ehlers–Danlos syndrome is known in an affected woman, counselling regarding the risk of pregnancy can take place before pregnancy and appropriate management and surveillance can take place during pregnancy. The development of multiple thromboses in an individual with vascular Ehlers–Danlos syndrome is a rare and unexpected complication as vascular Ehlers–Danlos syndrome is characterised by tissue fragility and increased risk of bleeding rather than formation of thromboses. Further data from large cohorts of patients with vascular Ehlers–Danlos syndrome are needed to assess the prevalence of this complication in individuals with vascular Ehlers–Danlos syndrome.

It is important knowledge for all health-care professionals that genetic testing on a large scale is a relatively recent development and it is worth referring an individual to the local genetic service when someone has persisting clinical features suggestive of an inherited condition even if this was seemingly excluded by previous (genetic) testing.

Declarations

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