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ONLINE CASE REPORT

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A combined vascular surgical and clinical genetics approach to diffuse aneurysmal disease

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ABSTRACT

We report two patients who presented with extensive aneurysmal disease, in association with minimal external physical signs. Patient 1 remained genetically undiagnosed despite multiple structural, biochemical and genetic investigations. He made a good recovery following surgery for popliteal and left axillary artery aneurysms. Patient 2 was diagnosed with vascular type Ehlers–Danlos syndrome, associated with a high degree of tissue and blood vessel fragility, and is being managed conservatively. Early multidisciplinary assessment of such patients facilitates accurate diagnosis and management.

KEYWORDS

Aneurysmosis – Marfan syndrome – Ehlers–Danlos syndrome – Loeys–Dietz syndrome – Genetics

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The presence of multiple arterial aneurysms is relatively rarely described, and has been previously reported in association with autoimmune vasculitis, infection and a small number of heritable disorders of connective tissue (HDCTs).[1] Vascular type Ehlers–Danlos syndrome (EDS) carries a high risk of morbidity and mortality associated with operative and intravascular procedures.[2] For this reason, the identification of individuals with a potential underlying genetic diagnosis is important for surgical planning. Both patients we present had no prior genetic diagnosis. We outline the differential diagnoses for patients with multiple aneurysms and discuss relevant HDCTs.

Case 1

A 54-year-old Sri Lankan man presented with painful, pulsatile, bilateral axillary masses. He had last visited a tuberculosis (TB) endemic area 13 years previously and had a prior diagnosis of latent TB, with a positive Mantoux test (22mm) 18 months before his presentation. There was no history of claudication or rest pain. Popliteal aneurysms were palpable but pedal pulses were strong, with no evidence of distal embolism or ischaemia.

Computed tomography angiography revealed aneurysms throughout the arterial tree, including both axillary arteries (Fig 1). Diffuse and unexplained aneurysms prompted urgent referral for a genetic and infectious disease review. Inflammatory, infective and autoimmune differential diagnoses were considered but serological and positron emission tomography screening and antineutrophil cytoplasmic antibody serology were negative. Although the patient had raised immunoglobulin E titres, *Strongyloides* was also excluded. He was negative for human immunodeficiency virus (HIV). He was treated with standard TB therapy (rifampicin, isoniazid) prior to surgery.

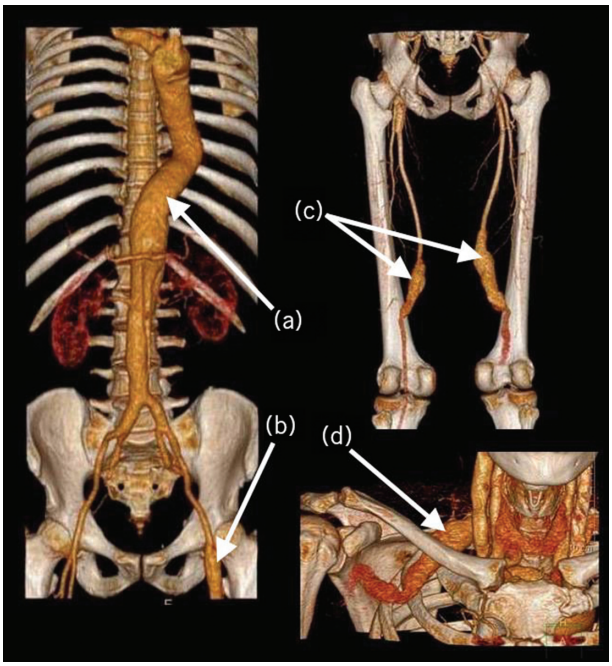

Figure 1 Patient 1: Three-dimensional reconstruction of computed tomography angiography showing an aneurysmal descending thoracic aorta (a), an aneurysmal left common femoral artery (b), aneurysms of bilateral midsuperficial femoral arteries (c) and an aneurysmal right subclavian artery (d)

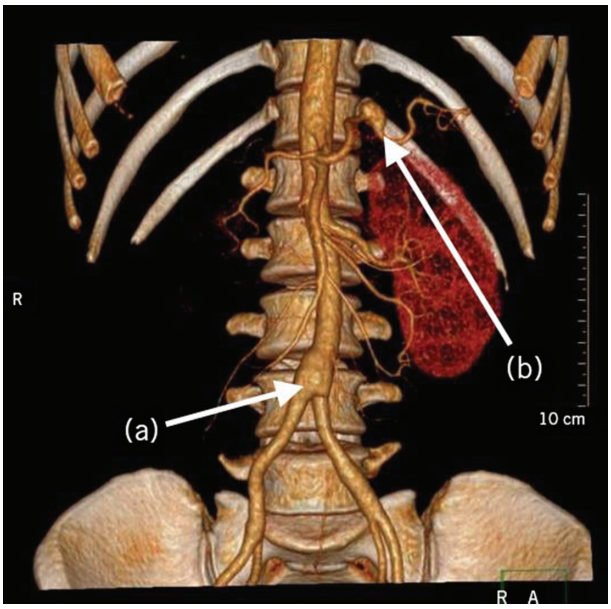

Figure 2 Patient 2: Three-dimensional reconstruction of computed tomography angiography showing incidental saccular aneurysms of the aortic bifurcation (a) and the splenic artery (b)

He underwent successful bilateral femoropopliteal bypass surgery and some months later, left subclavian-to-axillary bypass grafting.

Genetic assessment revealed no relevant family history; the proband was the third of nine siblings of unrelated parents. His skin appeared of normal thickness and integrity, and there was no skin thinning or acrogeria. There was mild bitemporal narrowing, with no other dysmorphism. There was no pectus deformity or generalised large or small joint hypermobility (Beighton score 0/9). The uvula and palate were normal.

Skin biopsy showed a mildly abnormal ratio of elastin to collagen. Ultrastructural studies revealed normal collagen fibril morphology and packing, with dilated endoplasmic reticulum of unknown significance. Collagen protein analysis from cultured skin fibroblasts showed a normal ratio of procollagen (III) and intracellular collagen (III). Popliteal artery histology revealed focal destruction of the muscular arterial wall, with chronic inflammation and thrombus. These findings are not typical of a primary vasculitis or known HDCT. Molecular genetic testing (sequencing and multiplex ligation dependent probe amplification) of *COL3A1*, *TGFBR1* and *TGFBR2* were normal/negative.

Case 2

A 36-year-old woman presented with primary infertility. Pelvic ultrasonography revealed a uterus didelphys, an atrophic right kidney and a dilated distal aorta. Magnetic resonance angiography (MRA) revealed saccular aneurysms of her aortic bifurcation and splenic artery (Fig 2).

Genetic assessment revealed was no relevant family history and her parents were unrelated. There was no prior history of ligament or tendon injury, unusual scars or severe ecchymosis although there was mild and lifelong easy bruising. The patient was non-dysmorphic, with a mild degree of skin thinning at the arms. Sequencing of the *COL3A1* gene revealed a mutation: c.1340G>A, p.(Gly447Asp). This confirmed the diagnosis of vascular type EDS. The combination of renal and uterine abnormality also raised the possibility of a small chromosome abnormality. Array comparative genomic hybridisation (Agilent [Santa Clara, CA, US] 8 x 60kb 60-mer oligo array, International Standards for Cytogenomic Arrays design 024612) showed a 188kb deletion at 16p12.1, of unknown clinical significance. (Parental samples were not available.) The patient was managed conservatively and referred onward for consideration of celiprolol therapy.

Discussion

Multiple aneurysms are reported commonly in patients presenting with a popliteal aneurysm and are more prevalent in male patients. In 571 patients with a unilateral popliteal aneurysm from the national Swedish registry, 28.1% had aortic aneurysms.[3] While atheromatous disease is the most common pathological correlate, other causes include infection and trauma.[4] In younger patients, the differential diagnoses include Behçet's disease and/or vasculitis.[5] Mycotic

Table 1 Beighton criteria for the diagnosis of vascular Ehlers–Danlos syndromes[7]

Major criteria	Minor criteria
Thin or translucent skin Intestinal, arterial or uterine fragility or rupture	Acrogeria
Extensive bruising	Hypermobile digits or other small joints
Characteristic facial features (pinched nose, hollow cheeks, prominent eyes, tight skin, lobeless ears)	Tendon or muscle rupture
	Talipes equinovarus
	Varicose veins
	Arteriovenous malformations
	Carotid cavernous sinus fistula
	Pneumothorax or haemothorax
	Gingival recession
	Family history of sudden death

aneurysms remain rare and are usually associated with salmonellosis, disseminated TB and/or HIV infection.[6] HDCTs associated with multiple aneurysms include vascular EDS, Loeys–Dietz syndrome (LDS), pseudoxanthoma elasticum (PXE) and arterial tortuosity syndrome (ATS).[1]

Vascular EDS (Online Mendelian Inheritance in Man® [OMIM] database #130050) is caused by a mutation of the *COL3A1* procollagen (III) gene on chromosome 2 with autosomal dominant inheritance. Mutations resulting in glycine substation disrupt type III collagen synthesis and excretion to the extracellular matrix, causing abnormal structural integrity to connective tissues, particularly blood vessels, colon and skin. In the largest cohort of cases to date, the median age of death was 48 years.[2] In 25% of cases, a major complication was present by the age of 20 years, and by age 40, this proportion increased to 80%. The majority of deaths were due to arterial dissection or rupture. Peripartum death due to uterine or vessel rupture occurred in 12 of 81 women.

Vascular EDS is one of six major types of EDS using the most recently described classification.[7] Features of vascular EDS are variable. They include severe arterial and tissue fragility, with arteries prone to aneurysm formation, dissection and rupture both spontaneously and during surgery. Diagnosis is indicated by the presence of two or more major criteria (Table 1). Nonsense mutations result in a milder external phenotype. However, they are still associated with a significant risk of vascular and hollow organ complications.[8] Individuals displaying minor criteria may warrant further investigation for this and alternative diagnoses while those with major features require confirmation by genetic testing.

Evidence for effective prophylactic and therapeutic interventions specific to this group of patients is limited owing to the rarity of the disease. A single randomised clinical trial of celiprolol versus non-treatment showed benefit in the prevention of complications and dissection in vascular EDS patients.[9] The study has been criticised because of the small number of patients included, some of whom did not have a genetically confirmed diagnosis. Nevertheless, the treatment benefits were significant, with reduction in arterial and hollow organ rupture.

Other HDCTs associated with multiple aneurysms include LDS (OMIM #609192) resulting from mutations in the *TGFBR1/TGFBR2* and *SMAD3* genes. These mutations cause abnormal cell signalling, which affects the development of vascular structures and musculoskeletal tissues. LDS patients may have aggressive aneurysm formation and arterial tortuosity beyond the aortic root, most commonly in the head, neck and thoracic aorta, a feature that is also associated with the Marfan syndrome. Facial dysmorphism affects up to 75% of individuals, with a cleft palate and bifid uvula forming major criteria for clinical diagnosis. Hypertelorism (wide spaced eyes), craniosynostosis, blue sclerae, micrognathia or retrognathia and strabismus are reported. Skin may be translucent, with visible veins, a history of easy bruising and poor wound healing.[10]

ATS (OMIM #208050) is an autosomal recessive disorder affecting the integrity of large and medium sized arteries as a result of elastic fibre disruption in the tunica media. Cases usually present in the paediatric age group, with adult cases reported occasionally.[11] A review of 35 cases reported prominent features including elongation, dilation and stenoses of large and medium sized arteries.[12] Elsewhere, abdominal hernias, joint instability, facial dysmorphism (facial elongation, micrognathia and beaked nose) and skin laxity are present.

PXE (OMIM #264800) results in mineralisation and subsequent fragmentation of elastic fibres, affecting the retina, dermis and medium sized arteries. The pattern of inheritance is autosomal recessive with a variable mutation in the *ABCC6* gene on chromosome 16. Clinical features include skin laxity and papular lesions affecting the flexures and skin creases. Visual impairment is caused by retinal haemorrhage subsequent to retinal mineralisation. Patients can also suffer from angina, claudication and rest pain. A review from 2013 identified peripheral arterial disease as a major component.[13]

Conclusions

These two cases illustrate the potential complexity with which patients with multiple aneurysmal disease present. A multidisciplinary vascular surgical and genetic assessment provides the optimal environment to treat this population. Many patients with different HDCTs have overlapping clinical and histological features, and in many individuals, the genetic cause remains unknown. In these situations, exclusion of

vascular EDS is recommended if at all possible as vascular surgical intervention could be more harmful than beneficial. Infective and inflammatory aetiologies may also be relevant, particularly in the absence of risk factors for atherosclerosis. Securing a genetic diagnosis is important, not only for preventing excess morbidity and mortality but also for effective medical management and for counselling of family members.

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