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Brief Report

Supravalvar aortic stenosis with supravalvar pulmonary stenosis and peripheral vascular stenoses

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Abstract A non-dysmorphic 10 month old female was discovered at surgery to have severe vasculopathy of both the systemic and pulmonary arteries. These findings were confirmed by pathologic examination. Follow-up angiography has confirmed multiple sites of vascular obstruction which appear to be worsening. Angioplasty has only partially relieved these obstructions. The pathology and possible etiology are reviewed.

Keywords: Supravalvar arterial stenosis; congenital heart disease

SUPRAVALVAR AORTIC STENOSIS IS A RARE BUT WELL recognised condition characterised by congenital narrowing above the level of the coronary arteries, usually involving the sinutubular junction. The combination of supravalvar aortic and pulmonary stenosis is rare in the absence of any well recognised syndrome. We describe herein a case of presumably sporadic supravalvar aortic stenosis, which includes the additional features of coronary arterial stenosis, stenoses of the central and peripheral branches of the pulmonary trunk, and multiple systemic vascular stenoses.

Case report

A term infant was clinically diagnosed with pulmonary stenosis shortly after birth, following discovery of a prominent systolic murmur in the neonatal period. At the age of ten months, echocardiography revealed the stenosis to be supravalvar, with a Doppler gradient of 70 mmHg. The echocardiographic examination also revealed supravalvar aortic stenosis, with a Doppler gradient of 100 mmHg across the sinutubular junction. Although asymptomatic, she was scheduled urgently for surgical repair, due to the significant stenosis of both great arterial trunks and evolving left ventricular hypertrophy. Cardiac catheterisation was not performed prior to surgery.

The patient has no family history of heart disease. Her mother, father, and older sister are all healthy. She has no dysmorphic features, no history of developmental delay, nor abnormal personality traits or hypercalcemia. Cytogenetic analysis was normal, and investigation for Williams' syndrome, specifically for 7q11.23 deletion using fluorescent in-situ hybridisation, was negative.

On surgical exploration of the aorta, diffuse luminal narrowing was found extending from the aortic root to the brachiocephalic artery. The thickness of the aortic wall measured at least 3.5 mm. The aortic valve, however, was normal, with three pliable leaflets. The pulmonary trunk was also found to be very thickened, but the pulmonary valve was normal.

Xenograft pericardial patches were used to enlarge the ascending aorta from the sinotubular junction to the arch, and the pulmonary trunk from the sinutubular junction to the bifurcation. At the time of surgery, biopsies were taken of both the ascending aorta and the pulmonary trunk for pathologic examination. Recovery was uneventful.

Pathologic evaluation of the aorta demonstrated mild changes, with the wall being thickened due to an increase in the number of elastic lamellas, which were regular and parallel (Fig. 1a–c). There were no inflammatory cellular infiltrates, increase in ground substance, or fibrosis of the media.

The pulmonary trunk (Fig. 1d–f) was noted to have a more distinctly abnormal structure than the aorta.

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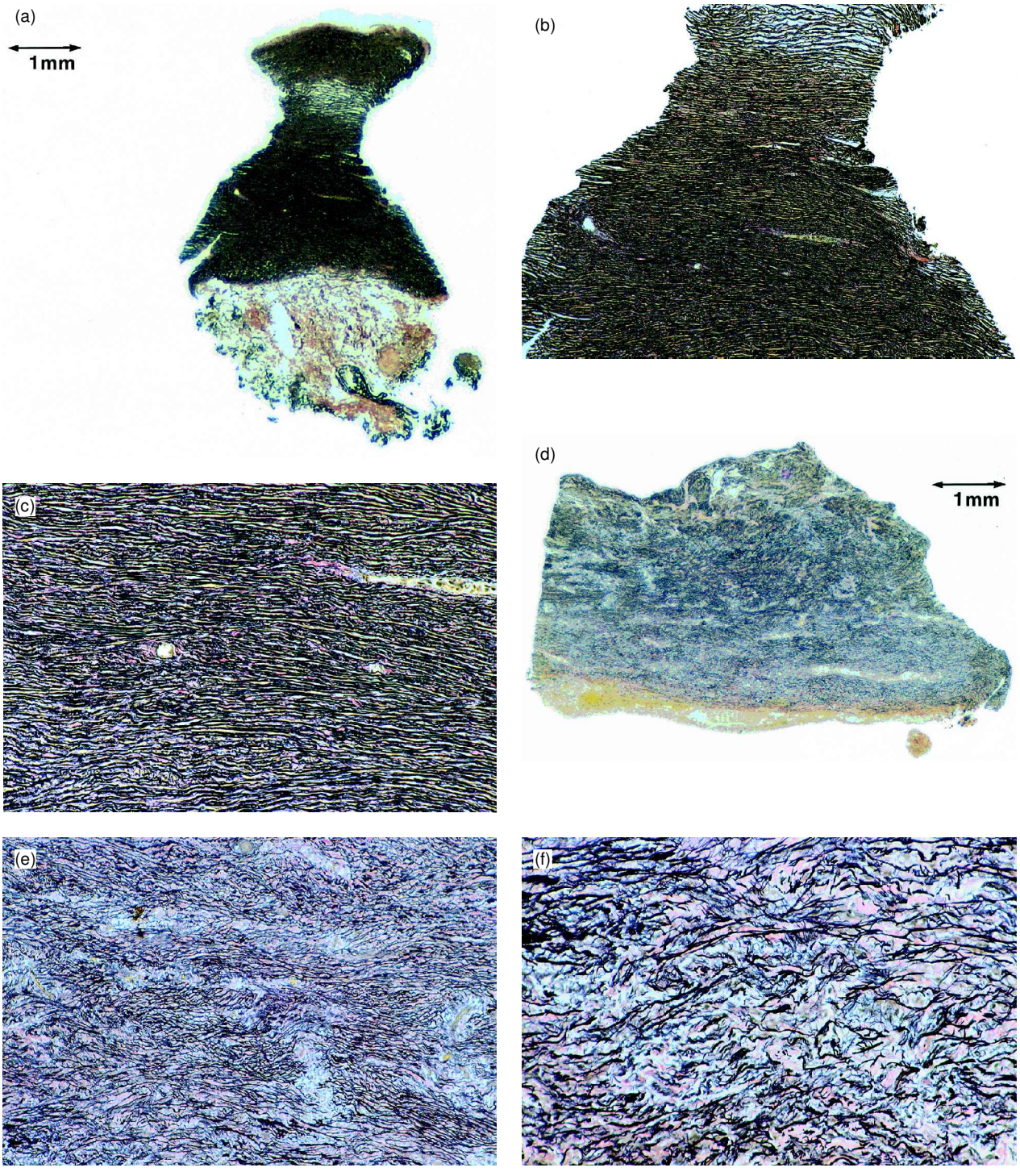

Figure 1.
Biopsies – all Movat stains. (a) Aorta – Full thickness biopsy of ascending aorta (magnification × 5). (b) Aorta – As in Fig. 1(a) at 20 × magnification demonstrating increased numbers of regularly arranged elastic lamellae. (c) Aortic media demonstrating increased numbers of generally parallel elastic lamina in the tunica media. (d) Full thickness biopsy of the pulmonary trunk, with increased thickness due to excessive and irregularly arranged elastic lamellas and fibrosis (magnification × 5). (e) Biopsy of the pulmonary trunk demonstrating irregularly arranged elastic lamellas and increased interstitial tissue of tunica media (magnification × 20). (f) The pulmonary trunk demonstrating irregularly arranged elastic lamellas and increased interstitial tissue of the tunica media (magnification × 50).

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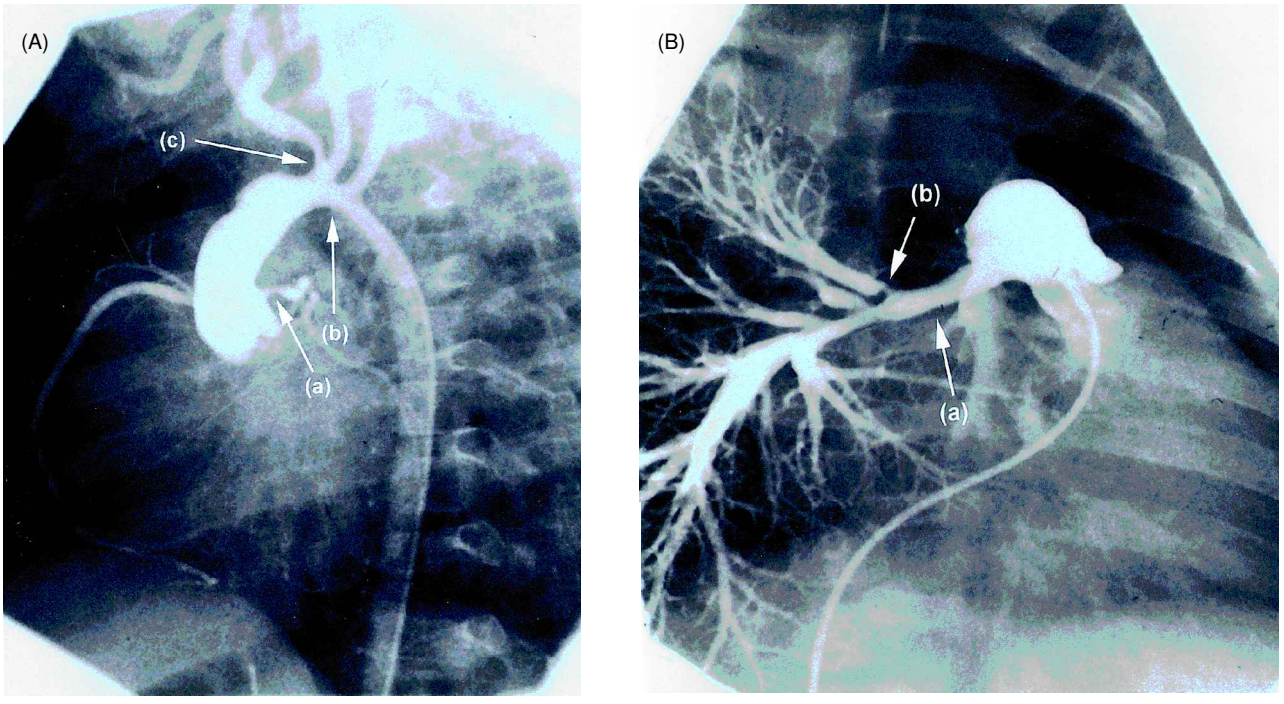

Figure 2.
(A) Left anterior oblique aortogram. Arrows denote stenosis of the main stem of the left coronary artery (a) and hypoplasia of the aortic arch (b) beyond the surgical patch. Note the stenosis in the brachiocephalic artery (c). (B) Right anterior oblique pulmonary arteriogram. There is diffuse hypoplasia of the right pulmonary artery (a) and severe obstruction in the segmental branch to the upper lobe (b).

The number of elastic lamellas was also increased, and they were haphazardly organised rather than regular and parallel. Patchy interstitial fibrosis was seen, along with areas with increased deposition of glycosaminoglycans. As in the aorta, no inflammatory cellular infiltrates, calcification, granulomas, or giant cells were present. The changes identified in both arteries were not characteristic of Takayasu's aortitis. Although similar to the arteriopathy seen in Williams' syndrome, the regular arrangement of elastic lamellas in the aorta and absence of valvar dysplasia, along with the negative probe for 22Q deletion and absence of other syndromic features, excluded a diagnosis of Williams' syndrome.

At the first cardiac catheterisation 2 months subsequent to surgery, other areas of stenosis were identified. These included the right and left pulmonary arteries, the aortic arch distal to the site of repair, the main stem of the left coronary artery, the brachiocephalic artery, the superior mesenteric, coeliac, and splenic arteries, and both renal arteries (Fig. 2a,b). There was a pull-back gradient of 35 mmHg over the transverse aortic arch. In follow-up Doppler studies, severe obstruction of the transverse aorta persisted, with velocities approaching 5 mm per second. A second post-operative catheterisation done 10 months after the operation, showed an increase in the gradient across the arch to 67 mmHg. Balloon angioplasties of the right pulmonary artery and a stenotic branch to the upper lobe were also performed, with minimal improvement in the calibre of the vessels. The abdominal vascular stenoses were less impressive, but the stenosis of the left coronary artery was worse. The stenosis at the brachiocephalic artery persists, with a gradient of 45 mmHg gradient over the stenotic area.

Discussion

Supravalvar aortic stenosis is an obstructive vascular lesion that can take the form of a discrete hourglass deformity at the sinutubular junction or diffuse aortic hypoplasia.[1] It often develops in combination with other vascular stenoses, including peripheral pulmonary arterial stenosis.[2–4] Supravalvar aortic stenosis is classically associated with Williams' syndrome, but is also seen as an isolated defect, both sporadically and in familial cases with autosomal dominant inheritance. Despite the distinction between isolated supravalvar aortic stenosis and the pattern associated with Williams' syndrome, the natural history is similar for both forms. In both, there may be accompanying peripheral pulmonary stenosis, as well as stenoses of other systemic arteries. Abnormalities of the elastin

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locus on chromosome 7 are present in both forms of supravalvar aortic stenosis.[5] Our patient clearly does not have Williams' syndrome based on clinical, pathologic, and genetic investigations. It is likely, therefore, that she has a sporadic form of supravalvar aortic stenosis, which probably represents a new mutation in the elastin gene, given that there is no family history of the disease.

In supravalvar aortic stenosis, pathologic studies of the medial layer of the aorta show focal to generalised haphazard arrangement of thick elastic fibers. There is excessive collagen, hypertrophied smooth muscle cells, and scant ground substance. This is in contrast to the organised parallel arrangement of these components in normal great arteries.[6] Inflammation is not typically seen. The pathologic findings in our patient, especially from the pulmonary trunk, are consistent with this description. The development of a parallel orientation of the elastic fibers, with intervening smooth muscle, ground substance, and collagen within the lamellar unit of the aortic media, is a normal feature of early intrauterine life. Although postnatal growth and aging are associated with progressive changes, parallel orientation of elastic elements is generally retained throughout life.[6]

Our case, therefore, involves isolated supravalvar aortic stenosis with coronary arterial stenosis and supravalvar pulmonary stenosis without Williams' syndrome. Obstruction of the left coronary artery is a recognised complicating feature of supravalvar aortic stenosis, and can cause sudden death in infants with this abnormality.[7–9] In the majority of cases, the stenosis is due to a thickening of the wall of the arterial orifice that is a response to the aortic component of the disease. Two other types of coronary arterial stenosis have been described in association with supravalvar aortic stenosis. Obstruction may result from distortion of the aortic valve, with adherence of the left coronary leaflet to the proximal edge of the sinutubular junction. Alternatively, diffuse narrowing can occur, as seen in our case, but this is very uncommon.

The remarkable feature in our case is the finding of supravalvar pulmonary stenosis. While stenosis of the peripheral pulmonary arteries and left coronary stenosis are well known features of Williams' syndrome, to the best of our knowledge, only rarely have other cases been described where supravalvar pulmonary and aortic stenosis appeared together.[4,5] In one of these cases, a fetus was detected by echo at 30 weeks with narrowing of both the aorta and the pulmonary trunk. The baby died shortly after birth, and the autopsy revealed diffuse tubular thickening, with luminal narrowing of the aorta, its branches, and the pulmonary arteries. Cytogenetic analysis demonstrated a chromosomal translocation involving the segment on chromosome 7 known to be responsible for Williams' syndrome.

In summary, our phenotypically and genotypically normal patient demonstrates a diffuse arteriopathy involving both the central and peripheral vasculature of both circulations. The etiology of this process, and its prognosis, remain uncertain. Future therapy may include additional attempted angioplasties of the affected vessels.[10]

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