Syndrome of Idiopathic Childhood Aneurysms: A Case Report and Review of the Literature

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ANEURYSMS in childhood are rare. In the thoracic aorta, they are usually associated with coarctation of the aorta or congenital aortic valvular disease. Aneurysms of the abdominal aorta, especially if multiple, may be due to an inherent defect of collagen biosynthesis, in particular collagen III in the arterial form of Ehlers-Danlos syndrome. Rarer causes include infection, neurofibromatosis, trauma from previous umbilical artery catheterization, tuberous sclerosis, and inflammatory causes that include Kawasaki disease, polyarteritis nodosa, Takayasu disease, sarcoidosis, and giant-cell arteritis. Rarely, no cause is identified and 14 cases of “idiopathic” aneurysms have been reported in the pediatric and surgical literature (1–14) (Tables 1,2). These cases may represent a distinct clinical entity, that of a syndrome of idiopathic childhood aneurysms. We report a case of a 5-year-old patient with multiple and widespread aneurysm formation.

CASE REPORT

A 5-year-old boy was referred to the surgeons with right arm swelling that had been present for 2 years, but which had recently increased in size. A second swelling had appeared in the left arm in the previous 6 months and the patient also had reported abdominal pain for 2 months. There was no history of joint dislocation, trauma, or bruising, nor was there any suggestion of bowel or limb ischemia. The patient had not been receiving any medication. There was no evidence of physical abuse. On examination, a large expansile abdominal mass was palpated, in addition to bilateral brachial masses. Blood pressure was normal. There was no clinical evidence of aortic valvular disease or coarctation. Apart from a slightly high palate, there were no obvious stigmata of Marfan syndrome, Ehlers-Danlos syndrome, or of a cutaneous vasculitis. His father, who also had a slightly high palate, was noted to have hypermobile joints. Screening of siblings yielded negative findings.

Ultrasound examination confirmed the presence of an abdominal aortic aneurysm and right and left brachial aneurysms. Angiography demonstrated 39 distinct aneurysms involving the abdominal aorta, left renal artery, superior mesenteric artery (Figs 1–4), and the arteries of the upper and lower extremities (Figs 5–12). The abdominal aortic aneurysm measured 8 cm in length, with a diameter of 4.5 cm, as demonstrated by sonography and computed tomography (CT). It arose just below the origin of the right renal artery, with a left lower pole renal artery arising from the aneurysm itself. The coronary and pulmonary arteries were normal. The distribution of the aneurysms was symmetric in the extremities, with clusters of aneurysms at the vessel branching points at the elbows, groins, and knees (Figs 5–7,10). The initial panaortogram did not include the cerebral circulation due to machine failure during the procedure. Contrast-enhanced computed tomography did not demonstrate an intracranial abnormality.

The patient’s blood count was normal, and the erythrocyte sedimentation rate, serum electrolytes, liver function, autoantibodies, serum complement levels, electrocardiography, and echocardiography were all found to be normal.

A structured investigative protocol, performed in conjunction with a national referral center, included evaluation of skin, muscle, tendon, radial artery and aneurysm tissue for routine histology, electron microscopy
and biochemical evaluation of radiolabelled collagen profiles. At the time of presentation, the collagen III level in cultured fibroblasts was borderline low. Subsequent measurements demonstrated normal levels of collagen III and normal α1 and α2 type I collagen profiles. Chromosome analysis of cultured cells demonstrated a normal male chromosome compliment. No deletion of the elastin gene was identified on chromosome 7.

Because of the risk of rupture, the abdominal aortic aneurysm was repaired. A straight aortic (12 mm) Dacron graft was placed from below the renal arteries to the aortic bifurcation. The right internal iliac artery was ligated and the right external iliac artery trimmed and repaired (Figs 2, 6). The lower pole left renal artery was ligated. No technical difficulties were encountered and the texture of the arterial wall was considered to be normal.

Histology and electron microscopy of the radial artery and abdominal aortic aneurysm were performed. The gross specimen demonstrated that the aneurysm consisted of a true diverticular out-pouching of the wall of the aorta at a site of loss of continuity of the internal elastic lamina. This demonstrated marked thickening and hyalinization of the intima, irregularity and partial disruption of the internal elastic lamina, and, in the tunica media, loss of elastic tissue and a reduction in smooth muscle cells. There was no evidence of an inflammatory response. At an ultrastructural level, there was fragmentation and condensation of the elastic fibers, an increase in the amount of collagen, and compression of smooth muscle elements. Stains for calcium were negative. Similar changes were identified in the main part of the vessel as were identified in the actual aneurysm. The findings were believed to be suggestive of a primary defect of elastic tissue. The radial artery biopsy demonstrated normal endothelium and elastic tissue.

The child was noted to be hypertensive in the immediate postoperative period. A dimercaptosuccinic acid isotope renal study demonstrated decreased perfusion of the lower pole of the left kidney. Subsequent color and Doppler spectral analysis demonstrated blood flow to this portion of the kidney. Blood pressure was controlled satisfactorily by means of medical treatment. Subsequent evaluations of renal vein renin levels demonstrated elevated renin production by the left kidney and suppressed levels from the right kidney. The left renal artery aneurysm was embolized approximately 21 months after first presentation. Follow-up sonography and dimercaptosuccinic acid and diethylenetriamine pentaacetic acid isotope studies demonstrated a nonfunctioning atrophic left kidney. Blood pressure remained controlled with use of two antihypertensive medications.

The patient re-presented 13 months later with persistent headaches. A left quadrantic homonymous
hemianopia was found on examination. Contrast-enhanced CT demonstrated interval development of a large aneurysm (1.5 × 1.0 × 1.0 cm) with adjacent hematoma, suggesting recent hemorrhage. Review of the contrast-enhanced CT at presentation (18 months earlier) still yielded negative findings. As well as the development of new aneurysms (Figs 2, 5–7, 12–14) up to 22 months after presentation, suggesting that the underlying cause, as yet undefined, was still active.

At the time of presentation, immediately after the aortic aneurysm repair, thrombosis of the right axillary artery occurred, requiring the administration of streptokinase. Thrombosis occurred again 7 months later. Recurrent embolic episodes subsequently occurred in both arms, requiring resections of brachial and axillary aneurysms and repairs with use of reversed saphenous vein grafts of the left and right arms 27 and 33 months after presentation, respectively. The patient recently experienced three embolic episodes involving his right arm, which have resolved spontaneously. The patient was maintained on antiplatelet therapy. Warfarin has been withheld to date.

Repeated angiography, performed on multiple occasions without complication, demonstrated both an increase in size of the existing aneurysms, as well as the development of new aneurysms. The patient was reviewed at 51 months after presentation, at age 9.75 years. Apart from a residual hemianopia, medically controlled hypertension, and embolic events to his right arm, he was well.

DISCUSSION

The spectrum and a clinicopathologic classification of childhood and congenital arterial aneurysms have been reported (15,16). It has been suggested by other authors that all of these “idiopathic” aneurysms are variants of Ehlers-Danlos syndrome, lacking the clinical skin and joint changes but with a propensity for aneurysm formation. An alternative approach would be to consider these cases as part of a syndrome of idiopathic childhood aneurysms. Additionally, it should be remembered that Ehlers-Danlos syndrome is, in reality, a heterogeneous group of clinically related but biochemically distinct disorders. Arterial complications are reported frequently in Ehlers-Danlos syndrome type IV, less commonly in Ehlers-Danlos syndrome type VI, rarely in Ehlers-Danlos syndrome types I, II and III, and reportedly are absent in types V, VII, VIII, and X. In Ehlers-Danlos syndrome type IV, and occa-
sionally type III, collagen type III mutations have been documented (17). In Ehlers-Danlos syndrome type IV, mutations in the COL3A1 gene affect the synthesis of type III procollagen. Collagen III is present in skin (especially fetal skin), blood vessels, and the uterus. While classical Ehlers-Danlos syndrome has a characteristic clinical phenotype, including thin hyperelastic facial skin, a prominent venous capillary pattern, ecchymoses, and hypermobile joints, Ehlers-Danlos syndrome type IV lacks the hyperextensible skin and hypermobile joints that might suggest the diagnosis. Hypermobility of joints, when present, is usually limited to the digits and rarely involves large joints. The diagnosis is based on the amount of collagen III in the skin or the production of collagen III by cultivated fibroblasts from skin. With normal levels of collagen III, our case is not a case of Ehlers-Danlos syndrome type IV. Three reports (4–6) documented patients with conditions similar to our patient, although none of these had intracranial aneurysms. An additional patient shared some features (9), while the remaining patients had significantly different features (1,3,7,8,11–14). In our review of the literature (Tables 1,2), we found that 93% of idiopathic aneurysms occur in children younger than 10 years old, with a mean age of 4.6 years (range, 0–14 years; 10 boys [71%], four girls). Aneurysm location (in decreasing order of frequency) included aortoiliac (10 of 15 [66%]), upper extremity (nine of 15 [60%]), renal (six of 15 [40%]), lower extremity (five of 15 [33%]), carotid and cerebrovascular (three of 15 [20%]), and mesenteric (two of 15 [13%]). Halpern et al (13), in a review of the literature, identified 12 previous cases and one new case. They, however, included one case with no pathology and two in which Ehlers-Danlos syndrome was a possible cause. The upper extremity arteries were involved in 92% of cases, the aorta and iliac arteries were involved in 92%, the renal and mesenteric ar-
teries were involved in 77%, the carotid and cerebral arteries were involved in 46%, and the lower extremities were involved in 39%. They noted that 69% of cases of aneurysms occurred in children younger than 10 years, and in families with no history of aneurysm disease. They, unlike our report, did not note a male sex predisposition. The symmetric distribution of aneurysms that we observed also has been noted previously (5,13).

Renovascular hypertension has been noted in previous reports (4,5,9), with a nephrectomy required in one case (4). As with our case, all were associated with both abdominal and intrarenal aneurysms.

Spontaneous thrombosis (5) and spontaneous rupture of aneurysms have been reported (4), both of which have occurred in our case.

It has been suggested that the syndrome of idiopathic childhood aneurysms may progress during active growth until adolescence, at which point it may stabilize; while no new aneurysms will develop, existing aneurysms may continue to enlarge for hemodynamic reasons (5).

Death, which can occur in both childhood and adulthood, surprisingly seems to be unusual (1,2,17,18,19). A formal clinicopathologic classification of childhood aneurysms proposed by Sarkar (15) included the following classes: class I = arterial infection; class II = giant-cell aortoarteritis; class III = autoimmune vasculitis; class IV = Kawasaki disease; class V = medial degeneration (Marfan and Ehlers-Danlos syndromes); class VI = medial degeneration (other causes); class VII = arterial dysplasia; class VIII = idiopathic (and congenital); and class IX = extravascular causes. The cases described in this report (Tables 1,2) did not demonstrate any evidence of inflammation or infection, particularly Kawasaki disease, and therefore do not belong to classes I–IV, or IX. Cystic medial necrosis was not described in any case, excluding classes V and VI. Sarkar described eight class VII aneurysms, seven renal and one common iliac aneurysm, but with none arising in the aorta. Three of four of the current cases had renal artery aneurysms, with associated hypertension. Dysplasia was not described. Therefore, within the limits imposed by incomplete clinical histories and histopathology, the 14 described cases are best considered as class VIII (idiopathic/congenital) aneurysms. Of the cases considered by Sarkar, all are part of our group. Three cases postdate his publication, while three are not referenced. He considered a case by Taheri (3) a class VI aneurysm, although there was no evidence of cystic medial necrosis. He also considered a case by Williams (4) as a class VI aneurysm. The pathology report suggests fibromuscular hyperplasia, a class VII aneurysm, but the aortic and iliac distribution would be atypical. Additionally, in a separate report, Sarkar (11), of the same case, subsequently acknowledged that while the pathology was reminiscent of Marfan disease, the patient had none of the characteristic stigmata. We, therefore, choose to consider it as an idiopathic aneurysm.

An alternative approach to the classification of pediatric aneurysms was proposed by Sterpetti (16). Type I aneurysms are considered to have a generalized disorder of the arterial tissue and usually have aneurysms at more than one site. Type II aneurysms have a localized defect of the arterial wall and do not have aneurysms at other sites. With the use of this classification, type I aneurysms would include cases 4–9, and 13, and type II aneurysms would include cases 1–3, 8, 10–12, and 14.

Histology of the vessels confirmed that all were true aneurysms, with no demonstrable etiology. A range of histopathologic changes were observed, including atheromatous change, intimal and medial proliferation, medial fibrosis, decreased and disordered elastic fibers, smooth muscle proliferation, mucopolysaccharide accumulation, and dystrophic calcification; with some variations noted between cases. Pertinent negative findings included absence of cystic medial necrosis, absence of inflammation, negative immunohistochemistry, and negative skin and fibroblast cultures. The
widely varying histologies seen with idiopathic aneurysms would not favor Ehlers-Danlos syndrome as a unifying pathology.

Elevated elastase activity has been reported (10,13), suggesting that an ongoing elastolytic process may be responsible for aortic aneurysm formation. Elastase levels have not been measured in this case. Increased amounts of elastase have been found in the aortic walls of patients with abdominal aortic aneurysms. This appears to occur as a result of smooth muscle cells and neutrophils responding abnormally to elastin breakdown products of atherosclerosis, producing more intracellular elastase and eventually leading to aneurysmal degeneration of the aortic wall (20).

There are multiple additional reports of cases that do not meet the criteria for an idiopathic childhood aneurysm. Sterpetti (16) reported the case of an aortic aneurysm in a 19-year-old man. The aneurysm was reported as showing histologic features of a long-term process, meaning that it probably started in childhood. Haynes (18) reported the case of a 32-year-old woman with multiple congenital aneurysms with vascular rupture. Although not investigated at an earlier age, this patient’s condition initially started when she was 16 years old. Takayanagi (19) reported a case of a ruptured abdominal aortic aneurysm in a 7-year-old girl, although it was believed that this might be due to Marfan syndrome. Howard (21) reported a case of a 5-year-old girl with a true aneurysm, a history of hypertension, and an intracerebral hemorrhage. However, while the histology of the resected kidney is extensively reported, the histology of the renal artery aneurysm is not mentioned at all and it is unclear whether it represented an idiopathic aneurysm. Gibson (22) reported the case of a ruptured aortic aneurysm in a 16-month-old boy. While likely congenital, the postmortem aorta was lost and no histopathologic evaluation was possible. Perry (23) reported the case of a 14-year-old boy with bilateral subclavian and axillary arteries, in whom spontaneous thrombosis occurred. Hypertension was also reported, but it was not stated whether this finding was investigated further. While believed to be congenital, this was not confirmed histologically. Colin (24) reported the case of an 18-month-old boy with presumed congenital brachial aneurysms, however, no histopathology is reported. Rose (25) reported the case of a 9-year-old boy with an abdominal aortic aneurysm, which was believed to be mycotic. Dorman (26) reported the case of a 10-month-old boy with bilateral axillary aneurysms due to fibromuscular dysplasia. Darden (27) reported a case of an abdominal aortic aneurysm in a 2.5-year-old boy. Although described as congenital, there were multiple other risk factors for aneurysm formation, including coarctation of the aorta, umbilical artery catheterization, and multiple arterial catheterizations. Todd (28) reported the case of a 6-month-old child with a “true” aneurysm, although this may have been related to umbilical artery catheterization. Bordeaux (29) reported a case of a 7-year-old girl with multiple aneurysms of the aorta, iliac, renal, and upper and lower limb arteries, but associated with an inflammatory syndrome. DeLetter (30) reported the case of an 18-year-old man who developed multiple aneurysms during a 30-year period. Although not investigated at an earlier age, a fusiform mass had developed during childhood after an accident. Subsequent angiography demonstrated a saccular aneurysm of the brachial artery.

While rare, childhood aneurysms merit thorough investigation and close follow-up. In our case, although the cranial CT had been normal only 12 months previously, a large aneurysm developed quickly and bled. Our case is unique in the wide distribution at such a young age and the rupture of an intracranial aneurysm. While the syndrome of idiopathic childhood aneurysms may represent an Ehlers-Danlos variant, lacking the clinical skin and joint changes, it may also represent a distinct clinical entity that will be defined by future developments in gene analysis.
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## References

14. Taketani S, Imagawa H, Kadoba K, Sawa Y, Sirakura R, Matsuda H. Id-


