CASE REPORT

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Familial Thoracic Aortic Aneurysms and Dissections

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ABSTRACT: Rupture of thoracic aortic aneurysms and/or dissections is not rare, occurring in approximately 0.6% of all medicolegal autopsies. Most forensic pathologists are aware of the association between thoracic aortic aneurysms/dissections and trauma, atherosclerosis, inflammation and Marfan syndrome. In this report, we discuss a familial form of thoracic aortic dilatation and/or dissection that is distinct from Marfan syndrome. In addition, we review the topic of thoracic aortic aneurysm and dissection and encourage family notification by forensic pathologists when familial forms of aortic disease are suspected at autopsy.

KEYWORDS: forensic science, forensic pathology, aorta, aneurysm, dissection, familial, autosomal dominant, Marfan syndrome

Autosomal inheritance of thoracic aortic aneurysms and dissections is known to occur in persons with Marfan syndrome, where the underlying genetic abnormality involves mutations of the fibrillin-1 (FBN1) gene on chromosome 15 (1). A distinct Marfan-like condition with thoracic aortic aneurysms and dissections results from a separate abnormality, located on an unidentified gene of chromosome 3 (locus 3p24-25) (2). Aortic dissection can also affect individuals with other recognizable connective tissue disorders, such as the Ehlers-Danlos syndrome, type IV (3). Despite these well-known associations, a majority of the thoracic aortic dissections discovered during medicolegal autopsies do not have obvious syndromal associations. While a large number of these cases are seemingly related to underlying degenerative processes such as atherosclerosis or inflammation, there remains a significant percentage of thoracic aortic dissections that apparently occur ''at random'' in individuals with no evidence of inflammation, significant atherosclerosis, or any well-known syndrome. In this report, we present an autosomal dominant condition characterized by thoracic aortic dilatation and/or dissection, but without associated cardiovascular or ocular features of the Marfan syndrome. In the family described, the condition is not linked to either the FBN1 or 3p24-25 loci.

Case Report

A 40-year-old male was at work and in his normal state of health when a co-worker playfully slapped him on the chest. Within seconds, he complained of midchest discomfort. He became pale and diaphoretic, and subsequently collapsed. He was emergently transported to a hospital emergency department where he was noted to be hypotensive. An echocardiogram showed a widened aortic root. As he was being prepared for an aortogram, he became unresponsive. Cardiopulmonary resuscitation was initiated, but all lifesaving efforts, including emergency thoracotomy, failed. A left hemothorax was identified during thoracotomy. The body was transported to the Dallas County Medical Examiner's Office for autopsy.

Death investigation revealed that several members of the decedent's family had died from or had been diagnosed with thoracic aortic dilatation and/or dissection. In fact, several members of the family were involved in a study at the University of Texas-Houston Medical School identifying families with familial thoracic aortic dilatation and dissection. The decedent had declined to have an echocardiogram performed. Extensive medical evaluation had determined that the family did not have Marfan syndrome. He was apparently in good health, with no history of hypertension.

At autopsy, the well-developed, well-nourished decedent weighed 175 lb and was 70½ in. tall. There was no arachnodactyly or other skeletal abnormalities noted on external exam. The ascending aorta was dilated (up to 13.5 cm circumference), with a 2.5 cm intimal tear located 2.5 cm from the aortic valve (Fig. 1). Aortic dissection extended distally into the upper abdominal aorta, (Fig. 2) as well as proximally to the aortic root, with associated pericardial and left pleural rupture. A combined total of 750 mL of blood was within the pericardial and left pleural cavities. The heart weighed 470 g, but was otherwise unremarkable. The thoracic and abdominal aorta and coronary arteries contained minimal atherosclerosis. The other vessels were unremarkable, as were most of the remaining organ systems. There was an incidental subcapsular well-circumscribed nodule within the right lobe of the liver. In addition, slight kyphoscoliosis was noted.

Microscopically, the aorta revealed mucinous degeneration with an increased amount of fibrosis and a relative decrease in the amount of elastic fibers (Fig. 3). The myocardium had mild interstitial and perivascular fibrosis with associated myocyte hypertrophy. The hepatic nodule was a lipoma.

The cause of death was cardiac tamponade due to hemopericardium due to thoracic aorta dissection and rupture due to familial thoracic aortic aneurysm and dissection following minor trauma to the chest. The manner of death was ruled accident.

Discussion

The most common cause of thoracic aortic rupture in the forensic setting is trauma, with aortic lacerations commonly occurring just

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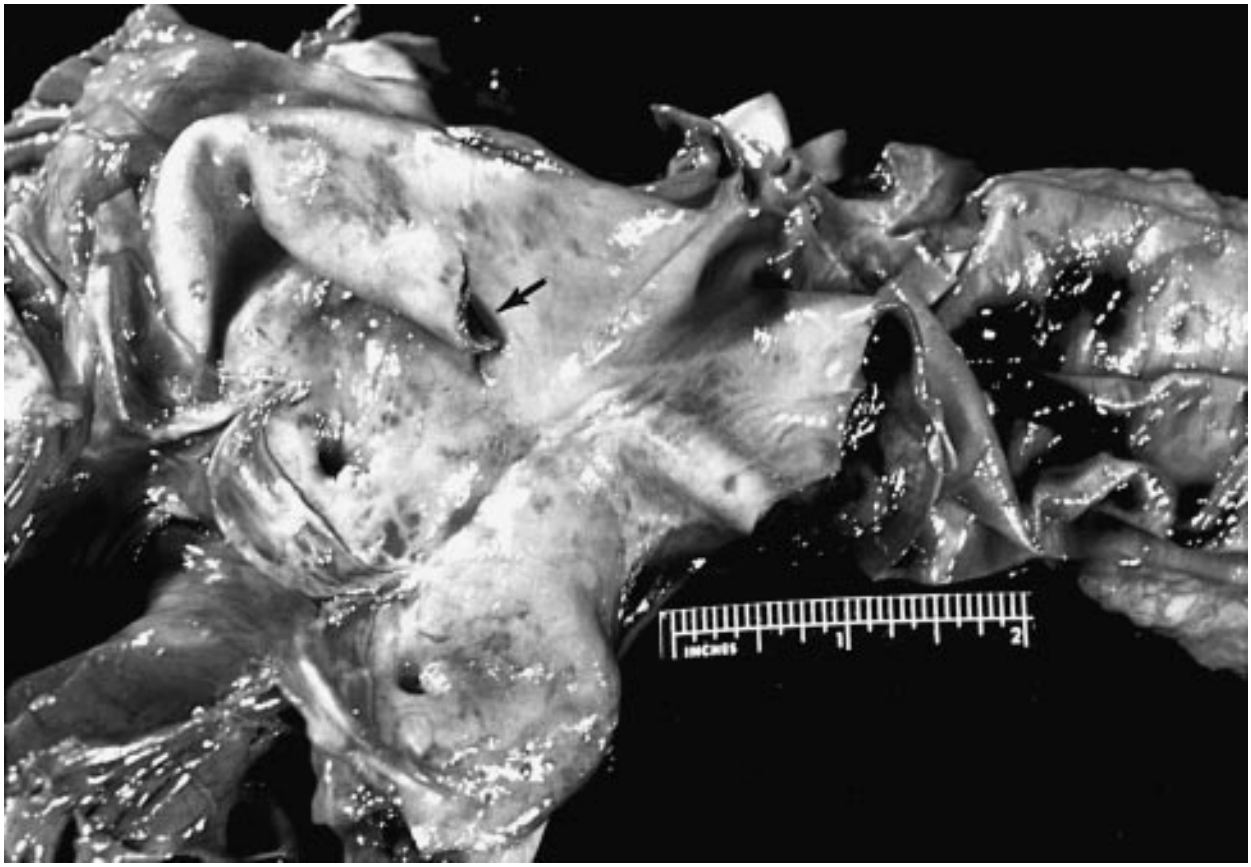

FIG. 1—*Photograph showing opened ascending aorta with intimal tear (arrow).*

distal to the left subclavian artery origin and ligamentum arteriosum in blunt force/deceleration injuries (4). Traumatic aortic rupture may also be iatrogenic, occurring most typically during intraaortic instrumentation/catheterization (5). Most traumatic aortic ruptures occur acutely; however, delayed ruptures occur occasionally, sometimes years after the initial injury.

Although trauma is responsible for many aortic ruptures seen by forensic pathologists, non-traumatic thoracic aorta rupture is not uncommon. At the Dallas County Medical Examiner's Office between 1991 and 1995 inclusive, during which time 13,551 medicolegal autopsies (including 4901 natural deaths) were performed, 78 cases of non-traumatic rupture of the thoracic aorta were recorded as the cause of death (approximately 0.6% of all autopsies and 1.9% of all natural deaths autopsied).

Non-traumatic thoracic aorta rupture is very frequently preceded by dilatation (aneurysm) and/or aortic dissection. Commonly recognized associations include atherosclerosis, hypertension, trauma, various inflammatory processes and Marfan syndrome (3,5,6). Despite these known associations, there remain a significant number of non-traumatic thoracic aortic ruptures that apparently occur ''at random'' with no significant atherosclerosis, other disease process, or obvious syndromal associations.

When a thoracic aortic dilatation and/or dissection is discovered at autopsy, the forensic pathologist should attempt to determine the underlying cause of the defect. Through historical information, careful evaluation for other abnormalities, and histologic examination, pathologists can sometimes determine the underlying cause (for example, atherosclerosis, syphilis, or Marfan syndrome). In other instances, the underlying cause is not elucidated, and the cause of death can be ruled ''ruptured thoracic aortic aneurysm,'' ''dissecting aortic aneurysm,'' or some similar descriptor. The ensuing paragraphs briefly describe a differential diagnosis for thoracic aortic dilatation and/or dissection.

A somewhat simplistic, but nevertheless useful, way in which to view thoracic aortic aneurysms is to separate them into those which are related to atherosclerosis and those which are not. Atherosclerotic aneurysms are more common in the descending thoracic aorta and often have concomitant hypertension (7), which is thought by some to play a contributory role in rupture (8). In addition, atherosclerotic aneurysms tend not to have associated aortic dissection and typically involve the descending thoracic aorta (type III dissections by the DeBakey classification) (7). They are less likely to rupture than non-atherosclerotic dilatations with associated dissection (7). In one study, atherosclerosis accounted for 15% of all thoracic aortic aneurysms (6).

Various degenerative and/or inflammatory processes are also known to result in thoracic aortic dilatation and rupture. The most widely known, but increasingly uncommon, cause is syphilis (6), where the gross appearance of the aorta (''tree barking'') and the microscopic appearance (obliterative endarteritis rimmed by a lymphocytic infiltrate with plasma cells) are pathognomonic (9). Aneurysmal dilation can also result from other types of aortitis (6), including polyarteritis nodosa, Kawasaki syndrome, other vasculitides, and so-called ''mycotic'' aneurysms, which result from other infectious organisms (9).

Marfan syndrome (MFS) is a relatively common, autosomal

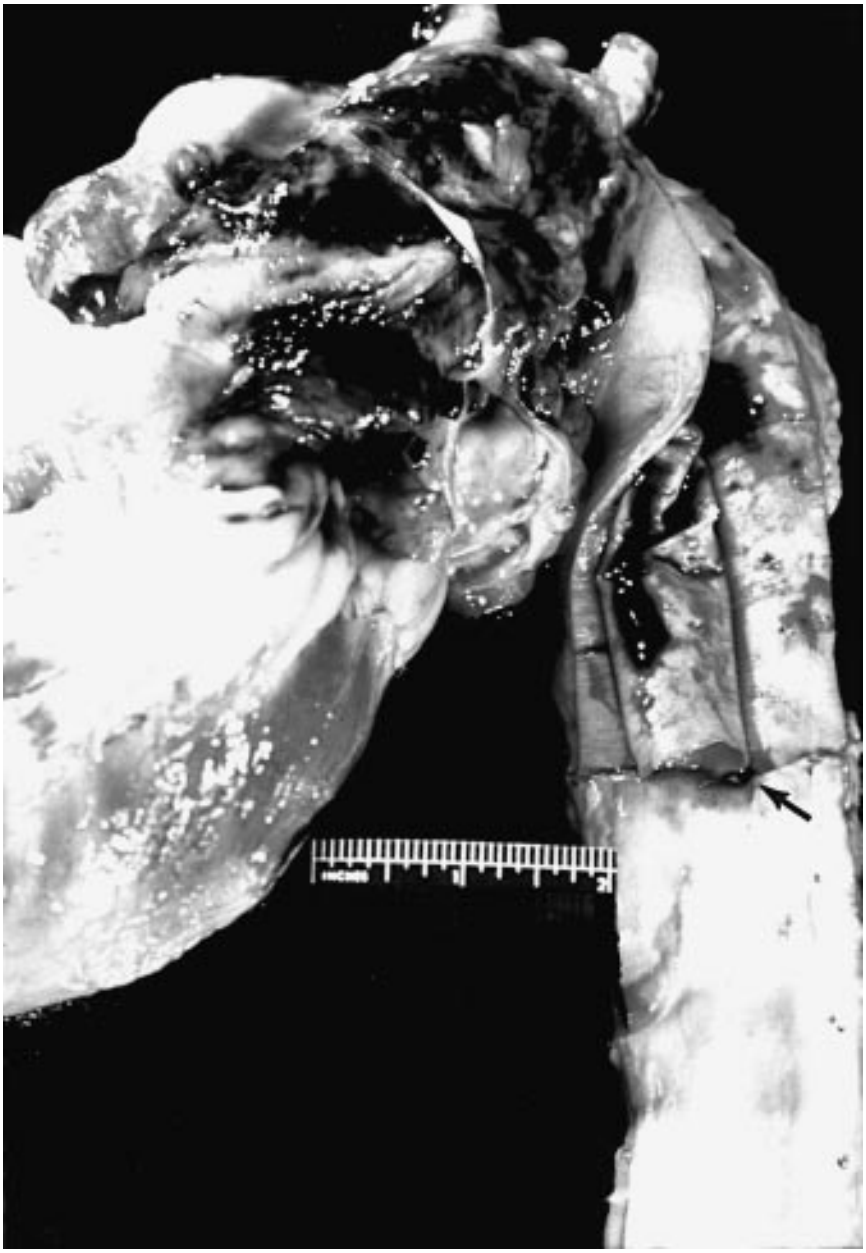

FIG. 2—*Photograph showing heart with hemorrhage surrounding the aortic root and extension of dissection into the previously opened descending aorta (arrow).*

dominant condition which results from defects in the fibrillin-1 (FBN1) gene, located on chromosome 15 (1). Marfan syndrome primarily affects the cardiovascular, ocular, and musculoskeletal systems (1,10–12), but other systems can also be affected (see Table 1) (11,12). Genetic mutations in the FBN1 gene result in the production of an abnormal fibrillin-1, a large glycoprotein (350 kDa) that is a component of the extracellular microfibril (1,10). Microfibrils are found in many tissues, either alone or intimately associated with elastin (1,10). The classic histologic appearance of the thoracic aorta in cases of MFS is cystic medial necrosis (5), which is discussed further in a subsequent paragraph. Marfan syndrome shows complete penetrance, but its clinical expression can be highly variable, making diagnosis difficult at times (1,10–12). At least 77 mutations of FBN1 have been identified in patients with Marfan syndrome, and all but 7 of them have been unique to a particular family (10). Approximately 25% of MFS cases result from new mutations (10).

Conditions related to the MFS, with some but not all of the features of classic MFS, can also result from other FBN1 mutations (1,3,10). It has been shown that FBN1 mutations can cause non-syndromal aortic aneurysms and dissections (3,13). A condition which is phenotypically similar to MFS, but without ocular or aortic manifestations, is congenital contractural arachnodactyly, which results from mutations in the fibrillin-2 gene on chromosome 5 (13,14). A distinct Marfan-like condition with thoracic aortic aneurysms and dissections and skeletal features of the MFS results from a separate abnormality, located on chromosome 3p24-25 (2).

Table 1 lists only certain manifestations of MFS. A more complete list and a detailed set of requirements for diagnosis are beyond the scope of this manuscript, but the criteria have been recently

published by De Paepe et al. (11). Suffice it to say that, with each organ system, there are major and/or minor criteria established; in order for a diagnosis of MFS to be made, a certain number of these criteria need to be met and the exact number required depends on whether or not another family member is affected (11). In all cases, homocysteinurea must be ruled out, since its phenotype is strikingly similar to that of MFS (12).

Another disorder that has been associated with thoracic aortic rupture is Ehlers-Danlos syndrome, type IV (3,5). In addition, certain endocrine disorders, Turner syndrome, polycystic kidney disease, pregnancy, and various aortic disorders, such as coarctation, hypoplasia, and bicuspid aortic valve, have all been associated with aortic dissection in various reports (5).

The role of hypertension in aortic disease continues to be debated. As previously stated, hypertension is thought to play a contributory role in atherosclerotic aneurysmal rupture (8). It is also thought to at least play a contributory role in aortic dissections (8). Clearly, a significant percentage of persons who develop thoracic aortic dilation and/or dissection have associated hypertension (6,8,15). In a study by Biddinger et al., 60% of persons with thoracic aortic dilation and 70% of those with thoracic aortic dissection had hypertension (15). Whether hypertension actually causes the dilation/dissection or only contributes to its manifestation (i.e., dissection/rupture) in persons already susceptible to dilation/dissection is not known with certainty. Theories which implicate hypertension as an underlying cause of aortic dilation/dissection suggest that elevated pressures directly induce structural weakness of the media and/or have an adverse effect on the vasa vasorum, resulting in suboptimal nutrition of the media (8). Whether or not hypertension is the underlying cause or a contributing factor in

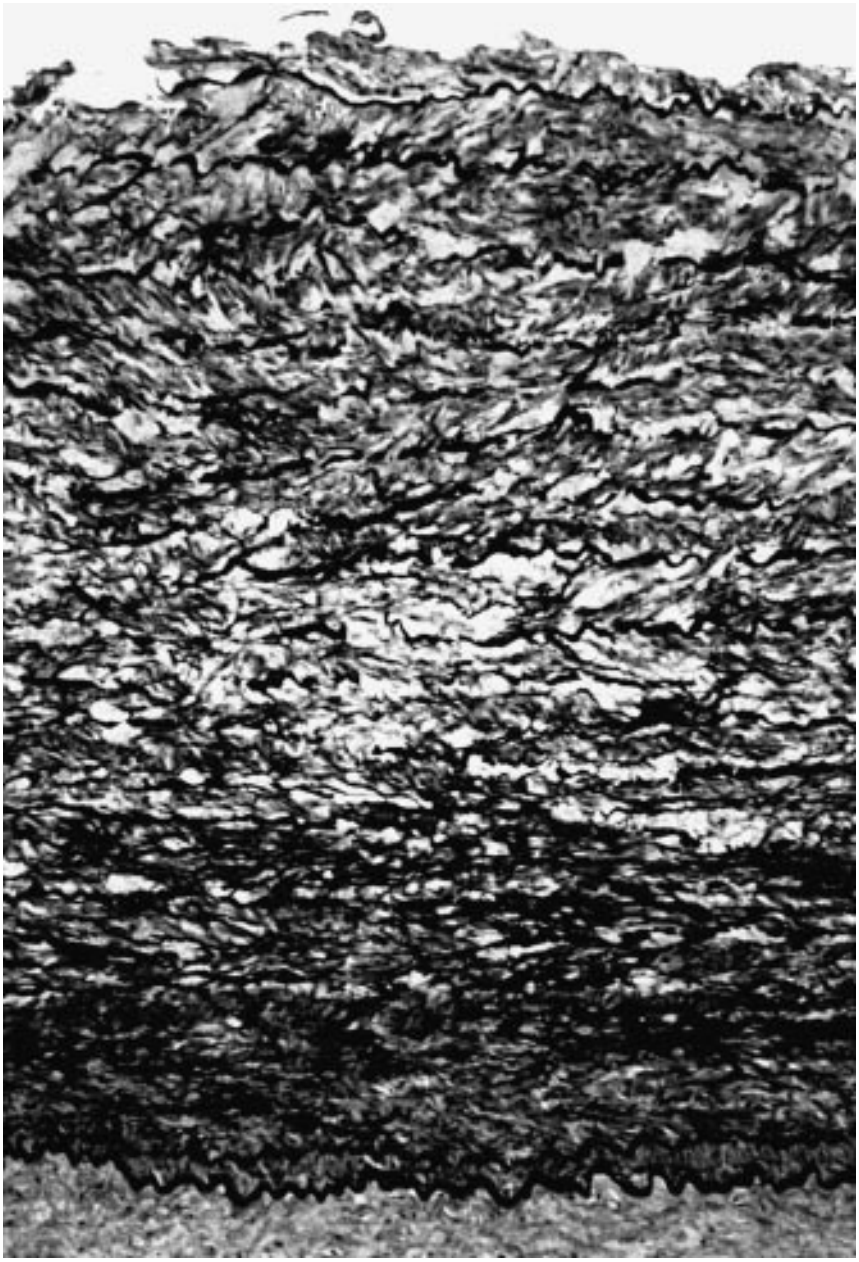

FIG. 3—*Photomicrograph of aorta showing fragmented elastic fibers (elastic stain, medium power).*

thoracic aortic disease, control of hypertension is an important part of the management strategy in persons susceptible to aortic dilation/dissection (8).

Although some thoracic aortic dissections occur as a result of a known underlying disorder or in association with some other condition, the fact remains that many occur without such associations. In the past, many of these were attributed to ''cystic medial necrosis,'' since the affected aortas often demonstrated CMN histologically (5,6,8), characterized by pools of basophilic ''mucoid'' material among fragmented elastic fibers (5). CMN is now generally regarded as the result of a degenerative process, whether it be from a true structural abnormality (i.e., MFS) or from the ''normal'' aging process (5). CMN, along with another relatively common histologic finding called ''laminar necrosis'' or ''medionecrosis'' (characterized by focal loss of nuclei and muscle fibers in a laminar pattern), is seen in many normal aortas (5). CMN, therefore, is not a cause of aortic dissection, although it can be seen in association with dissection. Put another way, it has become evident that the various degenerative processes responsible for producing aortic dilatations/dissections are not necessarily histologically specific or detectable (5).

Until more specific diagnoses can be made in theses cases with regard to the underlying cause of the thoracic aortic rupture (whether or not hypertension exists), forensic pathologists tend to list the cause of death as, ''thoracic aortic aneurysm and/or dissection,'' or some similar descriptive phrase (perhaps including hypertension as a contributory or underlying cause). It is likely that randomly occurring FBN1 mutations cause some of the isolated cases of thoracic aortic ruptures seen by forensic pathologists. Familial aggregation of thoracic aortic aneurysms/dissections with few or no features of MFS has also been described (1,3,10,15–17). In some of these cases, it has been shown that a mutation of the FBN1 gene is responsible for the aortic disease (3,13).

Recently, definite familial aggregation of aortic dilatation and/or dissection without FBN1 or 3p24-25 mutation has been described (13,18). So-called ''Familial Thoracic Aortic Aneurysms and Dissections'' (FTAAD) is a condition characterized by familial occurrence with autosomal dominant inheritance, marked variability in age of onset, and decreased penetrance, making identification of affected individuals difficult (18). Like Marfan syndrome, the characteristic pathologic finding is aortic dilatation and dissection, often with histologic evidence of cystic medial necrosis (18). Affected family members may demonstrate aortic dilatation alone, dissection alone, or a combination of both (18). Although musculoskeletal abnormalities such as scoliosis and inguinal hernias can occur in individuals with the disorder, the classic skeletal abnormalities associated with Marfan syndrome (arachnodactyly, joint laxity, etc.) do not occur (18). In addition, ocular abnormalities do not occur in FTAAD (18). Besides inguinal hernias and scoliosis, individuals with this disorder may have a propensity to develop cerebral artery aneurysms (18). Systemic hypertension may be present, but does not occur in everyone with the disorder (18). The underlying genetic and structural/protein defect responsible for this condition has not yet been elucidated, although studies are ongoing. A likely candidate for the defect is a component of the elastic fiber system. Once the defective gene(s) is(are) isolated, deoxyribonucleic acid base testing for mutations in these genes may be possible for diagnosis. Postmortem blood samples will be suitable for testing.

TABLE 1—*Marfan syndrome—possible manifestations.*

	Skeletal System	
Bone overgrowth	Ligamentous laxity	Chest-wall deformity
Spine deformity	Protusio acetabulae	Skull changes
Osteopenia	Congenital contractures	
	Cardiovascular System	
Aortic dilatation	Aortic dissection	Aortic regurgitation
Dysrhythmia	Endocarditis	Mitral valve prolapse
Other aneurysms		
	Ocular System	
Myopia	Subluxed lens	Shape changes
Tremulous iris	Retinal detachment	
	Integument System and Connective Tissue	
Striae	Inguinal hernia	Other hernias
	Neuromuscular Systems	
Dural ectasia	Dilated cisterna magna	Lumbosacral meningocele
Learning disability		
Hyperactivity	Myopathy	
	Pulmonary System	
Apical emphysematous blebs		Spontaneous pneumothorax

Modified from Mellion.

TABLE 2—*Causes of thoracic aortic aneurysm and/or dissection.*

Atherosclerosis
Hypertension
Inflammation (including syphilis and various vasculitides)
Infection (''mycotic aneurysms'')
Trauma;
—Blunt force/deceleration injuries
—Iatrogenic
Disorders of the elastic fiber system:
—FBN1 mutations (Marfans syndrome and variants)
—3p24-25 mutations
—Familial thoracic aortic aneurysms and/or dissections
Disorders of collagen:
—Ehlers-Danlos syndrome, type IV

Conclusion

In this report, we have reviewed the differential diagnosis of thoracic aortic dilatation and/or dissection (Table 2). We have also presented a recently described, but not yet fully-characterized, autosomal dominant condition, Familial Thoracic Aortic Aneurysms and Dissections. For the forensic pathologist, it is important to notify surviving family members when an heritable disorder is diagnosed or suspected at autopsy. Since FTAAD and several other disorders reviewed in this report are heritable and potentially life-threatening to surviving family members, forensic pathologists are encouraged to add thoracic aortic dilatation/dissection to their list of disorders requiring family notification. Persons who are known to be susceptible to thoracic aortic dilatation and/or dissection can implement various lifestyle changes (i.e., avoiding contact sports, controlling hypertension) and are easily followed by echocardiography so that premature death might be delayed or prevented (3).

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