Cardiovascular Pathology 25 (2016) 247–257

Contents lists available at ScienceDirect

Cardiovascular Pathology

Original Article

Consensus statement on surgical pathology of the aorta from the Society for Cardiovascular Pathology and the Association For European Cardiovascular Pathology: II. Noninflammatory degenerative diseases — nomenclature and diagnostic criteria

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ARTICLE INFO

Article history:
Received 11 November 2015
Received in revised form 3 February 2016
Accepted 8 March 2016
Available online xxxx

ABSTRACT

Surgical aortic specimens are usually examined in Pathology Departments as a result of treatment of aneurysms or dissections. A number of diseases, genetic syndromes (Marfan syndrome, Loeys–Dietz syndrome, etc.), and vasculopathic aging processes involved in vascular injury can cause both distinct and nonspecific histopathologic changes with degeneration of the media as a common denominator. Terminology for these changes has varied over time leading to confusion and inconsistencies. This consensus document has established a revised, unified

Funding: There were no sources of external funding.
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http://dx.doi.org/10.1016/j.carpath.2016.03.002

Keywords:
Aorta
Histopathology
Marfan syndrome
Loeys–Dietz syndrome
Bicuspid aortic valve
Medial degeneration
Cystic medial degeneration
Aneurysm
Dissection
Lamellar unit
Consensus document
Noninflammatory
Degenerative

nomenclature for the variety of noninflammatory degenerative aortic histopathologies seen in such specimens. Older terms such as cystic medial necrosis and medionecrosis are replaced by more technically accurate terms such as mucoid extracellular matrix accumulation (MEMA), elastic fiber fragmentation and/or loss, and smooth muscle cell nuclei loss. A straightforward system of grading is presented to gauge the extent of medial degeneration and synoptic reporting tables are provided. Herein we present a standardized nomenclature that is accessible to general pathologists and useful for future publications describing these entities.

1. Introduction and practical approach

Surgical specimens from the ascending and/or thoracic aorta are generally removed for aortic aneurysm or dissection, the consequences of a wide range of diseases, syndromes, or aging processes. Across this spectrum of disease, there is an overlapping collection of histopathologic changes to the aorta. Central to the histopathologic appearance of diseased aortas are degenerative changes of the media, specifically impacting the lamellar unit. The lamellar units are the primary constructs of the media composed of a single layer of smooth muscle cells, collagen, and proteoglycans sandwiched between elastic fibers [1]. Medial degeneration is the primary pathologic substrate in heritable connective tissue diseases of the aorta, and it occurs as a secondary phenomenon in many other pathological aortic conditions as detailed below. Over the years, the meaning of histopathologic terms used to describe medial degeneration has become confused and often misused. This consensus document is designed to cover three overarching themes. The first is to provide a unified nomenclature to the histopathologic findings of the noninflammatory degenerative ascending aorta. The second is to provide a new grading scheme to better and more consistently classify aortic lesions. The third is to briefly catalog the primary medial degenerative diseases of the aorta along with current knowledge regarding mutated genes and known associated histologic findings.

The approach to grossing an aortic surgical specimen was presented in an earlier consensus document [2]. The need to sample six or more full-thickness aortic segments is recommended because of marked local differences in the extent of degenerative medial changes. These differences relate to specific sites (proximal more than distal in the aorta and in the outer curvature more than inner curvature but marked differences may also occur randomly). In the case of noninflammatory diseases, the majority of the aortic samples are from the ascending aorta; however, aortic arch, descending aorta, and even thoracoabdominal or abdominal resection specimens are seen. In addition to taking six pieces of aorta in two cassettes for review, here we strongly recommend obtaining both a hematoxylin and eosin (H&E) stain and an elastic stain (Movat's pentachrome, Verhoeff–van Gieson [VVG], combined Masson's elastic [CME], etc.) for each case. A collagen stain (Masson's trichrome, etc.) is routinely ordered at many institutions but is not required unless findings of other stains suggest a need. A smooth muscle actin (SMA) immunohistochemical stain is also used at some institutions to more easily describe smooth muscle cell changes. If inflammation is noted in the specimen, we recommend following the approach outlined in the prior consensus document on inflammatory aortic pathology [3].

2. Histology of the normal ascending aorta

The aorta is an elastic artery of which the main structural components are elastin and collagen fibers, smooth muscle cells, and a proteoglycan-rich ground substance (Fig. 1). The thickness of the intima increases gradually with age; in newborns, the intimal layer is very thin, and endothelial lining is closely apposed to the first elastic lamella of the media (Suppl. Fig. 1). Due to a process of low-grade injury and repair over many years, the intimal layer gradually expands and is composed of extracellular matrix proteins (mainly collagen and mucopolysaccharides, as well as sparse mesenchymal cells, best visualized with an antibody for the alpha-1 isoform of actin (vascular smooth muscle cell actin, SMA-1 antibody). The media constitutes the largest component of the artery. The media is composed of concentrically arranged lamellar units of fenestrated elastic laminae that enclose smooth muscle cells, collagen fibers, and large amounts of proteoglycans (Alcian blue stains strongly positive in normal aorta) [1]. The lamellar units are approximately 11 μm in thickness. The number and thickness of lamellae varies by age and topographic site in the aorta; at birth, there are about 35 lamellar units, increasing to 50–60 in adult life. In contrast to muscular arteries, the aorta contains no prominent internal elastic lamina, nor does it have a distinctive external elastic lamina. Thus, these innermost and outermost elastic lamellae do not differ substantially from other laminar units of the media. The adventitia is composed of loosely arranged connective tissues, vasa vasorum, including lymphatic vessels and low numbers of perivascular leukocytes. In the aorta, these vasa vasorum normally extend into the outer third of the media and produce nonpathologic disruptions of the lamellar units. It must be noted that the "normal" aorta at older ages displays increasing degenerative changes of all structural components, as described later (age-related changes), related to longstanding (many decades) "wear and tear" (Suppl. Fig. 2).

3. Consensus terms and definitions of degenerative aortic histopathology

The earliest terminology of degenerative aortic histopathology was the classic description of medionecrosis by Erdheim in 1930 [4]. Since then, different groups have used a variety of terms to describe the histopathologic changes they have observed in the ascending aortas affected by diseases and aging [5–7]. Unfortunately, no specific terms have gained full acceptance and often a common term — such as "cystic medial degeneration/necrosis" — indicates disparate histopathologies in different studies. As a result, it is often not possible to distinguish subtle histopathologic variation among diseases [8].

The following terms and definitions are the result of an arduous consensus process to create a single unified and consistent set of terms to describe noninflammatory degenerative aortic pathologies. The members of this consensus committee were solicited from the membership of the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology. Consensus, but not necessarily unanimous agreement, was obtained for the terms and their use. Where there were sharper disagreements in the development of this document, they have been noted as such in the text. The opinions put forth here do not necessarily represent the opinions of all members of the Society for Cardiovascular Pathology or the Association for European Cardiovascular Pathology. These terms and definitions are recommended for use in general surgical

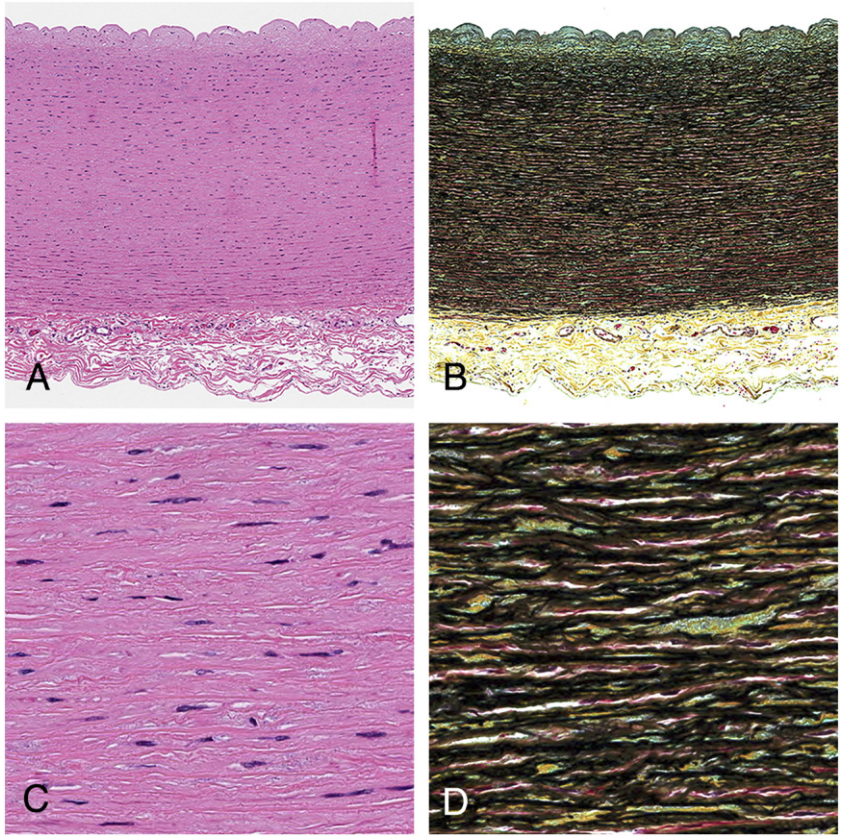

Fig. 1. Normal aorta, young adult. (A) Transverse section demonstrating all three aorta layers: intima at the luminal surface (top), media, and adventitia (50x, H&E). (B) On this stain highlighting elastic fibers, the intima is a distinctly paler layer than the media. The media consists of multiple lamellar units highlighted by the black lines of elastic laminae. There is an abrupt change at the boundary of the media and adventitia. The adventitia is mostly loose fibrous tissue (yellow). The vasa vasorum are distinct and of normal thickness (50x, Movat's pentachrome). (C) At higher magnification, the media shows distinct lamellar units with slightly more eosinophilic and refringent elastic laminae. The majority of the smooth muscle cell nuclei are seen in longitudinal orientation as this is a section perpendicular to the longitudinal axis of the aorta (500x, H&E). (D) The lamellar units in close up. One lamellar unit can be defined as the components between two layers of elastic laminae. These contents are (1) elastic lamina, (2) extracellular matrix [fibrous tissue (in yellow) and mucopolysaccharides (green/blue)], (3) smooth muscle cells (red cytoplasm and dark blue/burgundy nuclei), (4) extracellular matrix, and (5) another elastic lamina (500x, Movat's pentachrome).

pathology sign out and for categorizing histopathologies in case series and reports of aortic diseases. At this time, there is no definitive link between any of the terms below and a specific syndromic entity or secondary disease. However, this consensus terminology will support across-institutional and scientific reporting and will aid diagnosing these entities. Synoptic reporting tools and example histopathologic reports using these terms are presented as supplemental data files.

3.1. Top-line term: Medial degeneration

3.1.1. Definition

Overall degenerative alterations/damage to the aortic media resulting from the sum of individual histopathologic degenerative lesions (see below) affecting the lamellar unit (both cellular and extracellular) as observed on H&E, and stains to highlight elastic fibers and extracellular matrix material (such as VVG, Alcian blue, Movat's pentachrome, Masson's trichrome, CME).

3.1.2. Grading

None/mild/moderate/severe (see Table 1).

3.1.3. Notes

Medial degeneration is to be used as an overarching ("top line") term for any aortic surgical specimens that demonstrate the specific histopathologies described below. Grading of medial degeneration is based on the average overall severity of specific histopathologies as described, considering the worst area(s) sampled from multiple slides and aorta sections (see Table 1).

3.1.4. Individual components of medial degeneration

- Mucoid extracellular matrix accumulation
- Elastic fiber fragmentation and/or loss
- Elastic fiber thinning
- Elastic fiber disorganization
- Smooth muscle cell nuclei loss
- Laminar medial collapse
- Smooth muscle cell disorganization
- Medial fibrosis

3.2. Extracellular matrix alterations

3.2.1. Term: Mucoid extracellular matrix accumulation (MEMA)

3.2.1.1. Definition. An increase of medial mucoid extracellular matrix creating translamellar and/or intralamellar expansions including extracellular pools as noted on an H&E stain and/or a stain to highlight extracellular matrix material (Movat's pentachrome, Alcian blue, etc.) (Fig. 2).

3.2.1.2. Subclassification.

- **Intralamellar (MEMA-I):** the increase in mucoid extracellular matrix does not significantly alter the arrangement of the lamellar units.
- **Translamellar (MEMA-T):** the increase in mucoid extracellular matrix alters the arrangement of the lamellar units to varying degrees.

3.2.1.3. Grading (see below).

- Grade — mild/moderate/severe.
- Distribution — absent/focal/multifocal/extensive.

Table 1
Consensus grading scheme to evaluate medial degeneration

MEMA-Intralamellar	MEMA-Translamellar	Elastic fiber fragmentation and/or loss	Smooth muscle cell nuclei loss	Laminar medial collapse	Overall Medial Degeneration
Absent	Absent	Absent	Absent	Absent	**NONE**
Mild: Focal, Multifocal		Mild: Focal, Multifocal	Patchy: Rare	Thin: Focal	**MILD**
Moderate: Focal		Moderate: Focal			
Mild: Extensive	Mild: Focal, Multifocal, Extensive	Mild: Extensive	Patchy: Frequent	Thin: Multifocal, Extensive	**MODERATE**
Mod.: Multifocal	Mod.: Focal, Multifocal, Extensive	Mod.: Multifocal			
Sev.: Focal	Sev.: Focal	Sev.: Focal	Band-like: Frequent	Dense: Focal	
Moderate: Extensive	Moderate: Extensive	Moderate: Extensive	Patchy: Extensive	Dense: Multifocal, Extensive	**SEVERE**
Severe: Multifocal, Extensive	Severe: Multifocal, Extensive	Severe: Multifocal, Extensive	Band-like: Extensive		

1. Each component of medial degeneration is graded separately based on extent and severity. The presence of MEMA translamellar supersedes the need to grade MEMA intralamellar. The overall severity of medial degeneration is assessed on the cumulative severity across the four measures. The extent and severity of each histopathology is a guide for how each would contribute to overall medial degeneration

3.2.1.4. Notes. MEMA replaces a variety of terms used in the past such as "cystic medial necrosis, cystonecrosis, cystic degeneration, mucoid degeneration" which, while generally understood by pathologists, are inaccurate (Table 2). This histopathology can be subclassified and graded according to distribution, severity, and/or whether it crosses over multiple lamellar units as described [9]. The grading should be reported as mild/moderate/severe (Suppl. Figs. 3 and 4) and the distribution should be reported as focal, multifocal, or extensive. Some amount of intralamellar MEMA is always noted in cases of translamellar MEMA, and in cases of translamellar MEMA, it is not necessary to comment on the intralamellar MEMA, which is thought to be a less severe finding. It is strongly recommended that MEMA be graded and commented upon in all surgical pathology reports, when present.

3.3. Elastic fiber alterations

3.3.1. Term: Elastic fiber fragmentation and/or loss

3.3.1.1. Definition. Loss and/or fragmentation of elastic fibers of the media creating increasingly extended translamellar spaces, with absence of elastic fibers, and increased gaps in elastic fiber lamellae as identified on a stain for elastic fibers (Fig. 3).

3.3.1.2. Grading (see below).
- Grade — mild/moderate/severe.
- Distribution — absent/focal/multifocal/extensive.

3.3.1.3. Notes. This lesion may be seen in isolation or together with widening of intralamellar spaces. Due to the potentially patchy nature of this process, grading is essential to accurately describe this important finding (Suppl. Fig. 5). It is strongly recommended that elastic fiber fragmentation and/or loss be graded and commented upon in all surgical pathology reports, when present.

3.3.2. Term: Elastic fiber thinning

3.3.2.1. Definition. A thinning out of elastic fibers of the media that creates widening of intralamellar spaces, as identified on a stain for elastic fibers (Fig. 4).

3.3.2.2. Grading (see below).
- Grade — mild/moderate/severe.
- Distribution — absent/focal/multifocal/extensive.

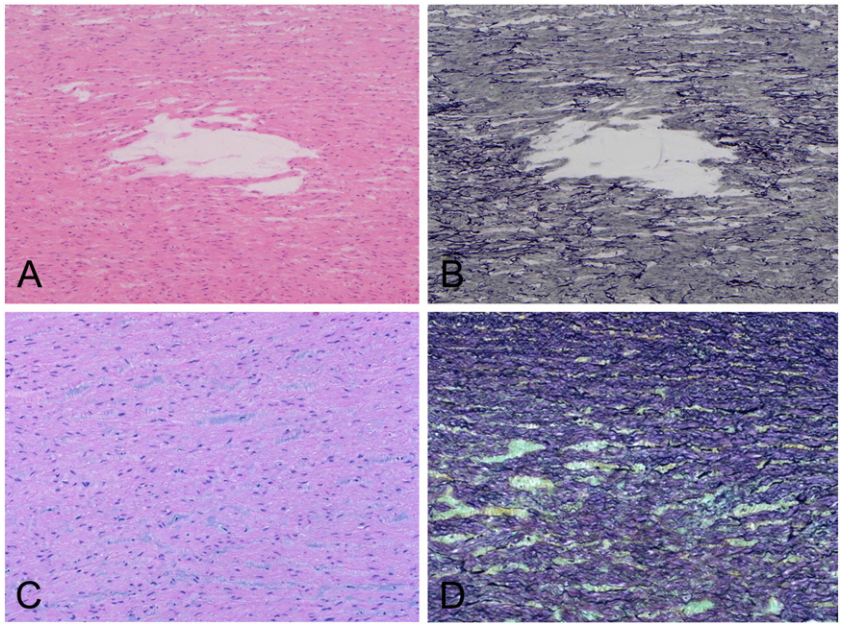

Fig. 2. MEMA. (A and B) Translamellar MEMA is a collection of mucoid material that breaks across lamellar units. (C and D) Intralamellar MEMA is an expansion of mucoid material that does not extend across the lamellar unit (H&E, Movat's pentachrome, 100x).

Table 2
Eponyms and historical nomenclature for selected histopathologic terms

Current term	Historical term(s)
MEMA	Cystic medial degeneration, cystonecrosis, cystic medionecrosis, cystic medial necrosis, medial necrosis, mucoid degeneration, medionecrosis, medial degeneration
Elastic fiber fragmentation and/or loss	Elastin fragmentation
Smooth muscle cell nuclei loss	Medionecrosis, smooth muscle cell necrosis, laminar medial necrosis
Laminar medial collapse	Laminar medial necrosis, laminar necrosis

3.3.2.3. Notes. A healthy aorta has dense elastic fibers comprising each lamella. This term describes the elastic network as being thinned at each lamella with narrower and more frayed apart elastic fibers. This entity may be associated with an increase in extracellular matrix material in the lamellar unit. The use of an elastic stain is essential to identify this lesion. This rarer entity should be commented upon, when present, but is not essential for routine surgical pathology reporting.

3.3.3. Term: Elastic fiber disorganization

3.3.3.1. Definition. Nonparallel arrangement/disarray of elastic fibers of the media as identified on a stain for elastic fibers (Fig. 5).

3.3.3.2. Grading (see below).

- Distribution — absent/focal/multifocal/extensive.

3.3.3.3. Notes. This rarer process is distinct from fragmentation and loss as the fibers acquire a more haphazard, poorly organized appearance, with loss of the usual parallel/concentric arrangement of elastic fibers within the lamellar unit. This finding is noticeable when at high power, and the orientation of the lamellar units parallel to the aortic lumen is lost. The use of an elastic stain is essential to identify this lesion. Disorganization of elastic fibers can be seen in conjunction with smooth muscle cell disorganization. A poorly oriented aortic specimen may appear to have disorganization and should not be confused with the real entity. This rarer entity should be commented upon, when present as

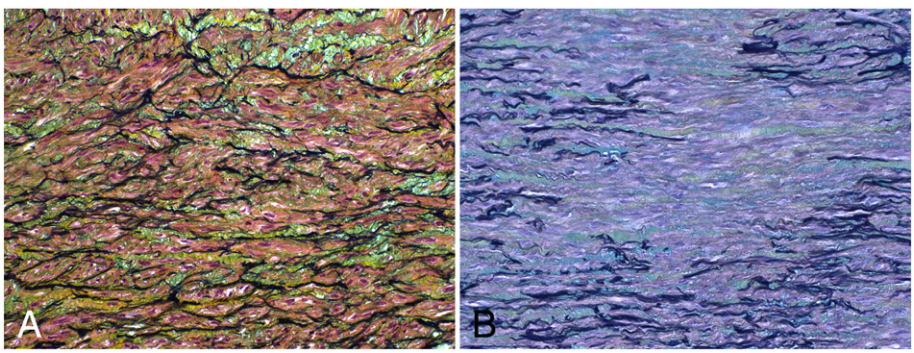

Fig. 3. Elastic fiber fragmentation and/or loss. (A) Fragmentation of the elastic fibers, where they no longer extend across the length of the image, is seen. (B) Complete loss of elastic fibers can occur (Movat's pentachrome, 400x).

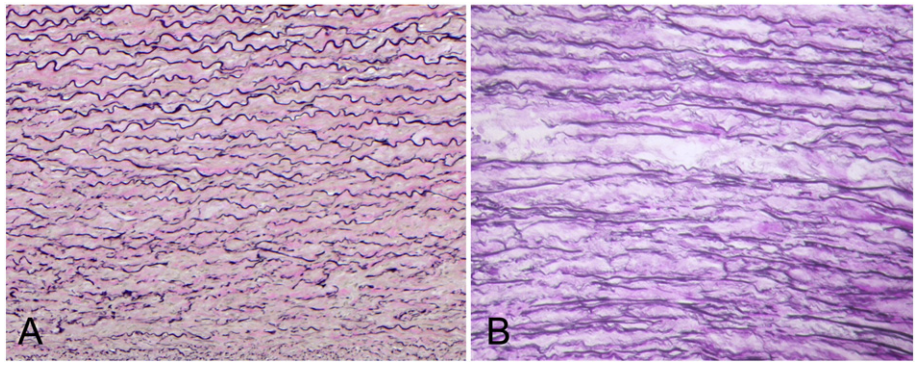

Fig. 4. Elastic fiber thinning. (A and B) In this entity, the elastic fibers are intact; however, they are thinned with a wide separation between them. This change would be seen in conjunction with an increase of extracellular matrix material (VVG, 20x).

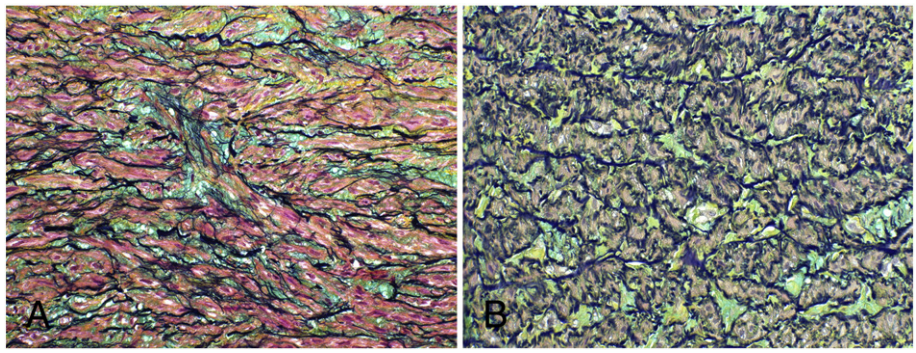

Fig. 5. Elastic fiber disorganization. At high power, there is a disruption in the organization of the wall, such that elastic fibers no longer adhere strictly to a circumferential course and can be oriented perpendicular to the lumen wall, which for these cases would be left to right. (A) Disorganization can be mild or (B) severe (Movat's pentachrome, 400x).

it represents a more severe feature of medial degeneration, but is not essential for routine surgical pathology reporting.

3.4. Smooth muscle cell alterations

3.4.1. Term: Smooth muscle cell nuclei loss

3.4.1.1. Definition. A region of the aortic media in which smooth muscle cell nuclei, involving multiple lamellae, are not clearly identifiable on an H&E stain (Fig. 6).

3.4.1.2. Grading (see below).
- Distribution — absent/rare/frequent//extensive.
- Type — patchy/band-like.

3.4.1.3. Notes. Smooth muscle cell nuclei loss replaces terms such as "medionecrosis" and "smooth muscle cell necrosis" that implied a loss of smooth muscle cells (Table 2). While the loss of a nucleus suggests the loss of the entire cell, this is not easily appreciated on an H&E stain. The shorter term "smooth muscle cell loss" was also considered by the consensus group and had many proponents, but the addition of "nuclei" was ultimately favored by the majority mostly as a histologic definition. Smooth muscle cell nuclei can be lost in patches or can be lost in a band-like pattern. This lesion can be noted in the absence of laminar medial collapse, described below. Both stains highlighting collagen and SMA immunohistochemistry (IHC) can be used to highlight smooth muscle cell changes (Suppl. Fig. 6). It is strongly recommended that smooth muscle cell nuclei loss be graded for distribution and commented upon in all surgical pathology reports, when present.

3.4.2. Term: Laminar medial collapse

3.4.2.1. Definition. Architecturally, a compaction of medial elastic fibers that creates thinning of the lamellar unit secondary to a band-like smooth muscle cell loss identified using a stain for elastic fibers (Fig. 7).

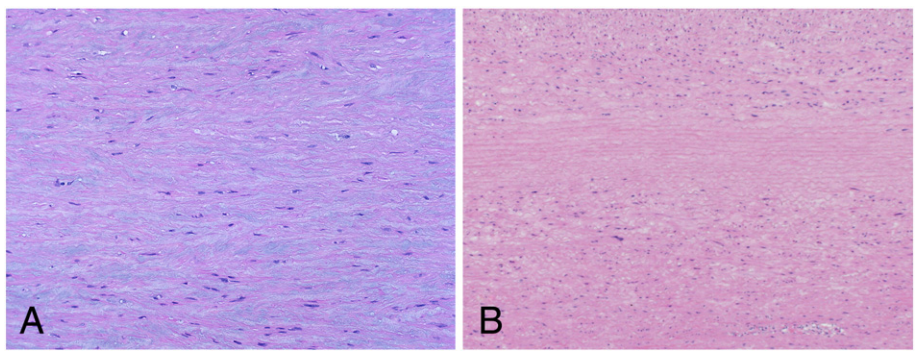

Fig. 6. Smooth muscle cell nuclei loss. Smooth muscle cells, as noted by their nuclei on an H&E stain, can be lost in a (A) patchy or (B) band-like fashion (H&E, 200×, 160×).

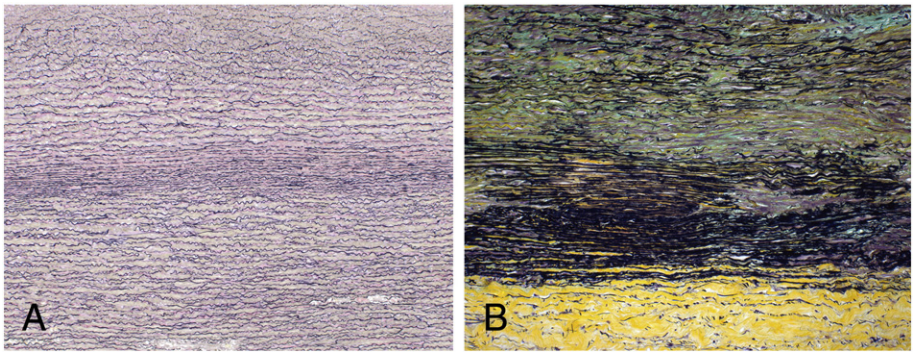

Fig. 7. Laminar medial collapse. In conjunction with a loss of smooth muscle cells in the lamellar units, the elastic fibers can collapse together. This banding pattern, only appreciated on an elastic stain, can be (A) thin or (B) dense (Movat's pentachrome, 100×, 40×).

3.4.2.2. Grading (see below).

- Appearance — thin/dense.
- Distribution — absent/focal/multifocal/extensive.

3.4.2.3. Notes. Laminar medial collapse replaces the old term "laminar medial necrosis" and is to be used only when an elastic stain has demonstrated elastic fiber compaction (Table 2). Laminar medial collapse appears as a darker band on an elastic stain as a result of a significant loss of intermixed smooth muscle cells. The collapse can be graded as thin or dense depending on the number of lamellar units involved in the process and the distribution should be reported as focal, multifocal, or extensive. It is strongly recommended that laminar medial collapse be graded and commented upon in all surgical pathology reports, when present.

3.4.3. Term: Smooth muscle cell disorganization

3.4.3.1. Definition. Nonparallel arrangement/disarray of smooth muscle cells of the media creating focal/multifocal disarray or sometimes nodular aggregates of smooth muscle cells (Fig. 8).

3.4.3.2. Grading (see below).

- Distribution — focal/multifocal/extensive.

3.4.3.3. Notes. This is a rare process proposed to be present in some genetic aortopathies mainly localized in the outer media. Disorganization can become extreme (Suppl. Fig. 7). Collagen staining and SMA IHC facilitates identification of the lesion. This rarer entity can be commented

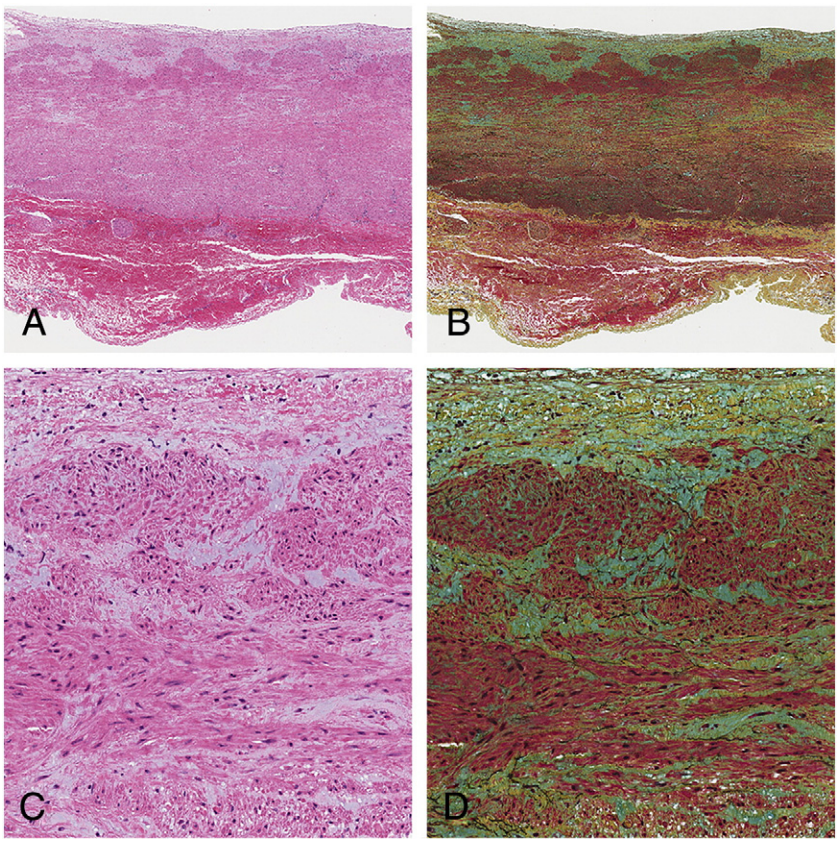

Fig. 8. Smooth muscle cell disorganization. (A) There is a conspicuous disarray of the bundles of smooth muscle cells throughout the media. (B) There is a slight thickening of the intima by mucopolysaccharide (blue-green ground substance)-rich extracellular matrix and small clusters of mucopolysaccharide accumulation in between the disorganized bundles of smooth muscle cells. Interstitial fibrosis (yellow) is also discernible at low magnification. There is a conspicuous decrease in the number of elastic lamellae. Organized lamellar units are practically absent. (C) At higher magnification, the disorganization of the smooth muscle cells is clearly shown. Note the orientation of the smooth muscle cells, ranging from transverse section of the smooth muscle cells to oblique to longitudinal orientation. Increased mucopolysaccharides (pale-blue areas) are present. (D) This high-power view shows disorganized smooth muscle cells, barely visible elastic laminae (black) as well as the abundant mucopolysaccharides in the interstitial space (H&E, Movat's pentachrome, 50×, 500×).

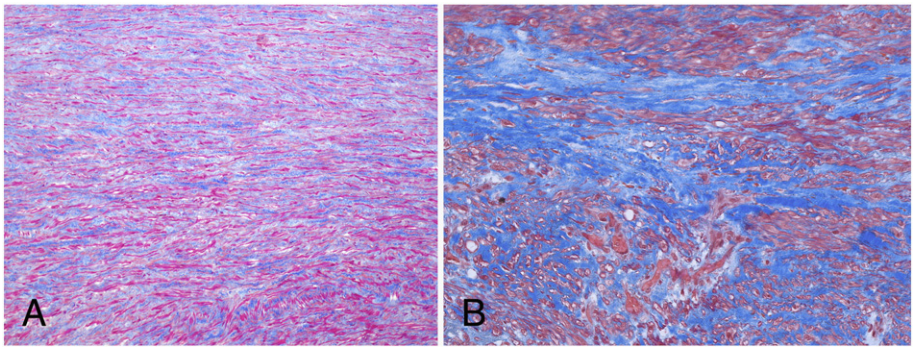

Fig. 9. Medial fibrosis. Excess collagen can be noted in some specimens. (A) An intralamellar accumulation of collagen (royal blue) leaves the lamellar unit intact. (B) Translamellar fibrosis disrupts the lamellar unit and can be associated with smooth muscle cell disorganization (Masson's trichrome, 100×).

upon, when present, but is not essential for routine surgical pathology reporting.

3.5. Collagen alterations

3.5.1. Term: Medial fibrosis

3.5.1.1. Definition. An increase in collagen fibers creating areas of substitutive fibrosis or a widening of intralamellar spaces in the media. This can be seen in conjunction with a loss to varying degrees of parallel arrangement of the elastic lamellae (or lamellar units) (Fig. 9).

3.5.1.2. Subclassification.

- **Intralamellar (I):** the increase in collagen does not significantly alter the arrangement of the lamellar units
- **Translamellar (T):** the increase in collagen is more scar-like altering the arrangement of the lamellar units

3.5.1.3. Grading (see below).

- Grade — mild/moderate/severe.
- Distribution — absent/focal/multifocal/extensive.

3.5.1.4. Description. This is a less common process in degenerative aortopathies that must be observed using a collagen stain. This entity can be commented upon, when present as it may represent more severe medial degeneration, but is not essential for routine surgical pathology reporting.

3.6. Grading system for overall medial degeneration

The degree of medial degeneration may vary considerably from very little to severe destructive alterations of the lamellar units of the aortic wall; thus, grading these lesions is essential. In addition, as these lesions are nonspecific for any single disease, collecting standardized data is the only way to be able to identify a more specific pathology picture in the future. Routine anatomic pathology evaluation of specimens does not permit complex quantitative grading systems or detailed morphometric analysis. Therefore, the Consensus Group considered a semiquantitative grading method preferable based upon severity and extent of each finding.

The overall top-line grading for medial degeneration (mild/moderate/severe) is obtained from a combination of both severity and distribution of the individual degenerative lesions. This is not simple because individual lesions often vary dramatically in severity and one alteration type may prevail over the others. Additionally, some findings are seen extensively in one segment of the resected aorta but are absent or minimal in others. Thus, there can be no strict definitions of medial degeneration severity, but this relies on the summation of the severity and extent of individual degenerative changes.

For routine surgical pathology reporting, we present a synoptic report (Suppl. File 1) and a table (Table 1) that provides a basis for characterizing the severity of overall medial degeneration using a mild/moderate/severe scale for severity and absent/focal/multifocal/extensive scale for distribution (extent). The extent of overall medial degeneration listed in Table 1 is thus a guide but not an absolute definition. This synoptic report also covers inflammatory disease of the aorta [3]. For the purposes of scholarship and advanced descriptions of aortic findings, we have provided a more extensive synoptic report (Suppl. File 2) that includes the entirety of the described histologic terms to be used in describing medial degeneration. Owing to the patchy nature of disease, grading should be performed at the most severe region from any one aortic segment from any of the reviewed slides. A schematic of severity and extent, examples of severity of medial degeneration, and mock surgical pathology reports are provided (Suppl. File 3 and Suppl. Figs. 8–12).

The degree of severity is rated as follows:

- Mild: lesion involves up to 3 lamellar units.
- Moderate: lesion involves 4–10 lamellar units.
- Severe: lesion involves >10 lamellar units.

The extent of individual lesions is graded as follows:

- Absent: the lesion type is not present.
- Focal: involvement of the media area up to 10%.
- Multifocal: multiple areas of involvement of >10–30% of the media area.
- Extensive: involvement of the media area >30%.

4. Age-related changes in the aorta

This new aortic pathology nomenclature described above has direct relevance on changes seen in both aging and syndromic causes of aortic dissection. Therefore, it is essential to understand the overall changes in aortic histology with age and accompanying risk factors.

With age, the aorta stiffens, dilates, develops histopathologic changes, and becomes tortuous with regional differences. A variety of risk factors contribute to aortic stiffness and propensity toward aneurysm and dissection with hypertension being the most critical factor [10]. The greatest difference in aortic stiffness occurs in the abdominal region, whereas the greatest difference in diameter occurs in the ascending aorta (annuloaortic ectasia) [11]. Fibrous intimal thickening (that is maximal in abdominal aorta), increased proteoglycans, and CD68-positive macrophages/histiocytes are usually observed in aging aortas [12,13]. These findings are also related to atherosclerosis. The thickened intima is infiltrated by mesenchymal cells that exhibit a proinflammatory profile [14].

4.1. Elastic component of aorta

Aging is accompanied by a relative loss of elastin content in human arteries as other matrix materials, primarily collagen, increase [13,15,16]. The remaining elastic fibers are more frequently fragmented and less cross-linked in the aged aorta as compared to younger

Table 3
Risk factors and histologic changes seen in ascending aortic aneurysms in the aged

Process	Associated risk factors	Associated histologic findings*
Aging	Smoking, hypertension, hypercholesterolemia, history of other aneurysms	MD++, MEMA-T+, SMCL+++, LMC++, EFF+, EFD+

Key: *: "+" denotes frequency of description in the literature. MD: Medial degeneration; MEMA-T: Translamellar MEMA; SMCL: Smooth muscle cell nuclei loss; LMC: Laminar medial collapse; EFF: Elastic fiber fragmentation and loss; EFD: Elastic fiber disorganization.

individuals [16]. Histologically, this appears as a thinner, more separated, and more fragmented elastic meshwork in the media. This histopathologic appearance of the media in older individuals is frequently comparable to the aortas resected from individuals with a genetic syndrome. This histopathology is reflected physiologically by a reduction in arterial elasticity and is prone to aneurysm [15].

4.2. Extracellular matrix

As the vasculature ages, neointimal proliferation and frank atherosclerosis may occur. Thus, a large amount of extracellular matrix, particularly collagen types I and III, are produced and they fill the subendothelial space [17]. Fragmentation of intralamellar elastic fibers results in separation of elastic laminas within the aortic media leaving gaps partially filled with proteoglycans [15]. Medial collagen, which is absent to rare in young aortas, increases with age. This is noted by an expansion of collagen staining within the intralamellar space by a collagen stain such as Masson's trichrome or similar. This collagen has been described as disorganized and unstructured, forming cloudy spaces rather than crimped or wavy fiber bundles [18].

4.3. Smooth muscle cells

Medial smooth muscle cells decrease in number in the aging aorta [19]. Medial smooth muscle cells also undergo age-related morphological changes toward a senescent phenotype. Sawabe proposed that smooth muscle cells of the media degenerate and reduce in number through apoptosis [15]. The loss of smooth muscle cells is often more apparent under neointimal plaques. This might be secondary to reduced diffusion of reagents from the lumen to these cells as the neointimal plaque increases in size. Extension of the vasa vasorum deeper into the media may preserve the integrity of these cells [20].

4.3.1. Conclusions

In the aging aorta, the elastic component, medial smooth cells, and extracellular matrix are progressively, negatively altered (Table 3). This results in the regenerative potential declining significantly with increased age promoting aortic aneurysms and dissections. Features of medial degeneration in the aging aorta bear close resemblance to medial changes in the genetic syndromes (see Tables 2 and 3). However, it should be noted that, in the case of genetic syndromes, these degenerative changes are more extensive, and they occur at an earlier age.

Our consensus group was evenly split on advocating when to suggest genetic causes in relation to medial degeneration. Those in favor support that, on average, aortae from individuals under the age of 40 years, with mild (or worse) medial degeneration should raise suspicion for an underlying genetic cause, whereas above the age of 50 years, a mild grade of medial degeneration can be attributed to aging and other long-term risk factors such as hypertension.

5. Genetic syndromes causing aortic aneurysm and dissection

A number of genetic syndromes are associated with ascending aortic aneurysm and resultant dissection. The most notable is Marfan syndrome (MFS), but other syndromes such as Loeys–Dietz syndrome (LDS) and Turner syndrome are relatively common causes of aortic aneurysms and dissections. Familial thoracic aortic aneurysm and dissection (FTAAD) is a collection of individuals who do not have a known, well-described syndrome yet have an aneurysm and affected first-degree relatives. All of these entities have been reviewed elsewhere in detail [8,21].

These genetic syndromes share some histopathologic features, primarily elastic fiber fragmentation and/or loss. Other histopathologic features are more frequent in certain syndromes (e.g., MEMA-T in MFS and MEMA-I in LDS) [9]. However, because of a lack of uniformity of terminology, sampling heterogeneity, and overlapping histologic findings of these syndromes, it is not yet possible to differentiate these syndromes based on any particular morphological patterns. A coherent nomenclature to aortic histology is necessary to best analyze the available specimens for pattern evaluation. A number of well-known syndromes along with their known genetic mutation, associated phenotypes, and associated histologic findings are listed in Table 4.

A common altered final pathway for many of these diseases appears to be altered TGF-β activity [21]. This has been demonstrated by

Table 4
Syndromic forms of ascending aortic aneurysm

Syndrome or disorder	Mutated gene	Associated phenotype	Associated histologic findings**
MFS	*FBN1*	Pectus excavatum, arachnodactyly, tall stature, lens ectopia, mitral valve prolapse	MD+++, MEMA-T+++, SMCL+, EFF+++
Vascular Ehlers-Danlos (vEDS/EDS-IV)	*COL3A1*	Thin skin with visible veins, easy bruising, visceral rupture, thin pinched nose, thin lips, prominent ears	MD+, MEMA-T+
LDS	*TGFBR1* *TGFBR2* *TGFB2* *SMAD3*	Hypertelorism, wide/bifid uvula, cleft palate, craniosynostosis, visceral rupture, easy bruising	MD+++, MEMA-I+++, MEMA-T+, EFF+++, EFD+
Turner syndrome (TS)	Monosomy X	Female sex, webbed-neck, short stature, lymphedema	MD++, MEMA-T+++
Arterial tortuosity syndrome (ATS)	*SLC2A10*	Extreme vascular tortuosity, dolicocephaly, malar hypoplasia, joint laxity	MD++, EFF+++
Shprintzen-Goldberg (SG)	*SKI*	Features of MFS, LDS + mental retardation, severe hypotonia	
Autosomal dominant polycystic kidney disease (ADPKD)	*PKD1*	Renal cysts, renal failure, saccular intracranial aneurysms	MEMA+
FTAAD	*MYH11*† *ACTA2*†	Patent ductus arteriosus Moyamoya, livido reticularis	MD++, EFF++

Key: **: "+" to "+++" represents frequency of description in the literature. FBN1: Fibrillin 1; COL3A1: Collagen 3A1; TGFBR1: Transforming growth factor beta receptor 1; TGFBR2: Transforming growth factor beta receptor 2; TGFB2: Transforming growth factor beta 2; SMAD3: Mothers against DPP homolog 3; SLC2A10: Glucose transporter 10; SKI: SKI protooncogene; PKD1: Polycystic kidney disease 1; MYH11: Myosin heavy chain 11; ACTA2: Actin, alpha 2, smooth muscle; MD: Medial degeneration; T: translamellar, I: intralamellar; EFF: Elastic fiber fragmentation and/or loss; EFD: Elastic fiber disorganization; SMCL: Smooth muscle cell nuclei loss; LMC: Laminar medial collapse; "†" represents a minority of involved individuals.

enhanced pSMAD2/3 immunostaining in specimens from individuals with MFS, LDS, and other diseases [22,23].

6. Congenital diseases involving the aorta

Several congenital disorders can also result in altered histology of the ascending aorta. Below is a brief description of these entities in relation to aortic alterations.

6.1. Bicuspid aortic valve with aneurysm (BAV)

Bicuspid aortic valve is a relatively common congenital cardiovascular anomaly, which occurs in 1–2% of the population. A subgroup of patients develops an aneurysm of the aortic root, with an estimated 6-fold increased risk of dissection. The grade of medial degeneration is mild in most cases, but rarely it can be extensive. Degenerative changes of the pulmonary trunk have also been reported in the setting of BAV. NOTCH-1 mutation is associated with bicuspid valve disease and calcifications, but not generally associated with an aneurysm phenotype. MEMA-T, smooth muscle cell nuclei loss, laminar medial collapse, and elastic fiber fragmentation and/or loss are all commonly reported [24].

6.2. Coarctation of the aorta

Coarctation of the aorta, defined as a narrowing of the aorta distal to the left subclavian artery, is present in 5–10% of all cases of congenital heart disease. Of patients with an aortic coarctation, 50–80% will also have a congenitally bicuspid aortic valve, although most bicuspid aortic valves are not associated with coarctation. Coarctation is generally identified and repaired in infancy. It is rarely associated with aortic dissection. Extensive MEMA and elastic fiber fragmentation have been reported [25].

6.3. Tetralogy of fallot

In patients with tetralogy of Fallot who have undergone repair, a subset of individuals develop insidious aortic root dilatation later in life. At the time of surgical repair, these aortae demonstrate a significant medial degeneration, highlighted by absence of lamellar units, increased elastic fiber fragmentation, MEMA, and medial fibrosis [26].

6.4. Diverticulum of Kommerell

A diverticulum of Kommerell is a dilated lesion generally occurring in the setting of right-sided aortic arch at the site of origin of the left subclavian artery. However, it may also refer to aortic dilatation at the site of origin of an aberrant retroesophageal right-sided subclavian artery where it is thought to be a remnant of the right dorsal aorta. In a study of 18 patients with diverticulum of Kommerell, MEMA was noted in all specimens while some specimens additionally showed atherosclerotic plaques or intimal hyperplasia [27].

7. Nongenetic, noninflammatory causes of aortic aneurysm and dissection

7.1. Hypertension

As mentioned earlier, the most important risk factor for development of medial degeneration, particularly among the aged, is systemic hypertension [10]. In a large series from the Mayo Clinic, hypertension was present in ~60% of patients with a surgically resected thoracic aneurysm due to noninflammatory aortic disease [5]. Pathophysiologically, its effect can be interpreted as resulting from altered hemodynamic forces and possibly accelerated or aggravated aging processes of the aortic media. In the absence of hypertension or known genetic syndromes or congenital abnormalities afflicting the aorta, some individuals still develop aneurysms and dissections related to pregnancy or specific lifestyle factors including cocaine abuse and weightlifting.

7.2. Cocaine

Chronic cocaine abuse results in a loss of aortic elasticity and increased stiffness leading to aneurysm [28]. Although it is a rare cause of aneurysm, in certain populations where cocaine use is endemic, it can be common among young male hypertensive individuals [29]. Resected aortae in these cases are reported to have MEMA [8].

7.3. Strenuous exercise/weight lifting

Severe physical exertion, particularly weightlifting or isometric exercise, can cause elevations in blood pressure over 300 mmHg. This causes dangerous levels of wall stress. In individuals with aneurysm for any reason (genetic?), there is a propensity to rupture the aorta [30]. In the few published cases, MEMA was described frequently [8].

7.4. Pregnancy

Pregnancy-related changes may accelerate the development of histologic alterations in the aortic wall similar to those seen in medial degeneration. Pregnancy-related aortic dissection is overwhelming seen in women with an underlying predisposition such as MFS or bicuspid aortic valve and aneurysm. However, in any pregnant women, a risk of rupture is seen when the aortic diameter is >4 cm. It is believed that hormonal effects lead to fragmentation of fibers and reduced acid mucopolysaccharides [31].

8. Conclusion

Aortic resections contain important diagnostic information that has been difficult to understand, convey, and share due to a variety of nonstandardized nomenclatures. This consensus grading system provides a standardized and unified method for surgical pathology reporting and also for research studies on noninflammatory degenerative aortic pathology. We anticipate that its use will allow the recognition of histopathologic patterns characteristic of specific genetic aortic syndromes, which will lead to improved clinical decision making. However, developing such a systematic description using standardized terminology is only the first step. The next step will be to evaluate large numbers of aortas using these standardized criteria via the synoptic reporting tool and determine the extent to which specific histopathologic findings correlate with both disease entities and outcomes. Such studies on hundreds of aortic resection specimens are now in progress. Only then can we understand the utility of this surgical specimen as a tool for surgeons and geneticists.

Acknowledgements

There were no sources of external funding. The authors thank Norman Barker for assistance with several figures.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.carpath.2016.03.002.

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