Cardiovascular Pathology 30 (2017) 6–11

Contents lists available at ScienceDirect

Cardiovascular Pathology

Original Article

Histopathologic differences partially distinguish syndromic aortic diseases

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ARTICLE INFO

Article history:
Received 2 April 2017
Received in revised form 3 May 2017
Accepted 31 May 2017
Available online xxxx

Keywords:
Marfan syndrome
Loeys–Dietz syndrome
Aortic aneurysm
Nomenclature
Histopathology
Bicuspid aortic valve
MEMA

ABSTRACT

A variety of syndromic diseases such as Marfan syndrome, Loeys–Dietz syndrome, and bicuspid aortic valve with aneurysm along with risk factors of smoking and hypertension result in ascending aortic aneurysms and dissections. Historically, a complicated variety of terms have been used to describe a range of histopathologies that are present in resected specimens. As a result, no consistent patterns of histopathology have been reported. We used the recent Society for Cardiovascular Pathology/Association for European Cardiovascular Pathology consensus statement on nomenclature and diagnostic criteria for noninflammatory aortic disease to blindly evaluate 148 surgically resected specimens. We found that overall patterns of histopathologic changes could separately cluster bicuspid aortic valve and nonsyndromic subjects from Marfan and Loeys–Dietz subjects. Marfan syndrome cases significantly had more overall medial degeneration and mucoid extracellular matrix accumulation than other syndromes. Smooth muscle cell nuclei loss was a feature of aging and not a feature of Marfan or Loeys–Dietz syndrome subjects. We conclude that a consistent use of histologic and histopathologic descriptors can help discriminate different etiologies of ascending aortic aneurysms.

1. Introduction

The description of histopathologic changes found in the ascending aortic dates back to at least 1930 when medionecrosis was described by Erdheim [1]. Since that time, numerous syndromic and nonsyndromic causes of ascending aortic aneurysms have been described [2,3]. Therefore, there has been interest in determining if certain histopathologic descriptors correlate with specific entities and if these terms could be used to help clinicians determine the etiology of a patient's aneurysm [4,5].

A variety of histologic and histopathologic naming conventions have been used over the past 40 years [5–7]. However, none of these methods has been consistently used, resulting in a confusing set of descriptions that vary between studies, case reports, and case series [2]. The Society for Cardiovascular Pathology (SCVP) and the Association for European Cardiovascular Pathology (AECVP) created a working group, which, over a series of meetings held across many years, developed two consensus statements regarding inflammatory diseases and noninflammatory degenerative diseases of the ascending aorta [8,9].

The noninflammatory degenerative disease consensus statement was primarily tasked with developing a consistent and rational set of well-defined histologic and histopathologic descriptors of findings observed in the ascending aorta. This included the development of a new term — mucoid extracellular matrix accumulation (MEMA) — which replaces a variety of terms based on Erdheim's original cystomedionecrosis [9]. MEMA was segmented into an intralamellar process occurring within a lamellar unit or a translamellar process extending across multiple lamellar units. Other major descriptors such as elastic fiber fragmentation and/or loss (EFFL), smooth muscle cell nuclei loss (SMCNL), and laminar medial collapse (LMC) are little changed from prior definitions.

We hypothesized that this new set of definitions and diagnostic criteria could distinguish between causes of ascending aortic aneurysms. To test this, we obtained 148 surgical pathology cases from the case files of The Johns Hopkins Hospital and ascertained a variety of histologic and histopathologic findings on each case in a blinded fashion.

2. Materials and methods

2.1. Case selection

The study includes 100 consecutive noninflammatory aorta specimens from the Johns Hopkins Hospital in-house surgical pathology service taken from May 2014 to June 2015. The study was subsequently enriched to include an additional 29 resections from cases with Marfan

The authors declare that they have no conflict of interest.

Sources of support: none.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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http://dx.doi.org/10.1016/j.carpath.2017.05.008
1054-8807/

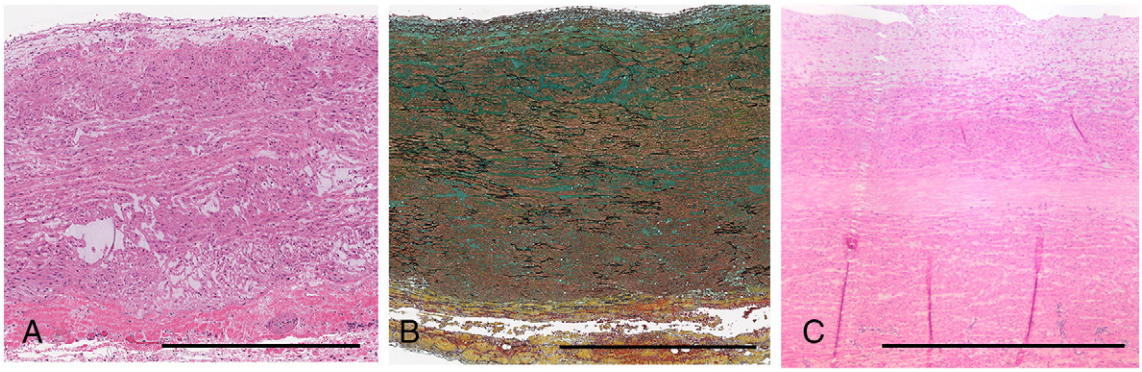

Fig. 1. Representative images of major histopathologic changes. (A) Severe, extensive translamellar MEMA. (B) Severe, extensive EFFL. (C) Band-like, extensive SMCNL. Bar=1 mm. For a more extensive collection of images, please see [9].

syndrome (MFS) and 19 cases with Loeys–Dietz syndrome (LDS) so that the study includes a total of 148 resections obtained from 2004 to 2016. Sections of aorta were taken randomly from the surgical material. These aortic fragments were not oriented by the surgeons. Hematoxylin and eosin (H&E) and Movat Pentachrome stains were evaluated for each case using standard staining methods. In addition to the presence or absence of a syndrome, demographic and basic phenotype data were collected for each case (age, sex, race, *Z*-score for aortic root size, and indication for surgery). An aortic root *Z*-score is a measure of aortic root dilatation corrected for by subject height, weight, and age [10,11]. The study was approved by the Johns Hopkins Hospital internal review board.

2.2. Review and scoring

Using the new AECVP and SCVP consensus nomenclature and standard definitions [9], each case was scored separately for extent and severity (where possible) across 12 features [overall medial degeneration score (MDS), MEMA, EFFL, elastic fiber thinning (EFT), elastic fiber disorganization (EFD), SMCNL, LMC, smooth muscle disorganization (SMD), atherosclerosis, dissection, vasa vasorum medial thickening, and adventitial fibrosis; Fig. 1]. This was based on the Supplemental File 2 scoring system of the consensus document [9]. The overall MDS, severity, and extent of the features were scored on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe and 0 = none, 1 = focal, 2 = multifocal, and 3 = extensive) with three exceptions. SMCNL severity was scored on a scale of 0–2 (0 = none, 1 = patchy, and 2 = bands). MEMA, which was categorized into two types (intralamellar and translamellar), was scored on a scale of 0–6 for both extent and severity by multiplying the extent and severity by 1 for cases with intralamellar MEMA and by 2 for cases with translamellar MEMA under the premise that translamellar MEMA is a higher-grade lesion. LMC was scored on a scale of 0–2 (0 = absent, 1 = thin, and 2 = dense). Each case was scored for the above features, blinded to the patient's clinical information, by two observers from a pool of one cardiovascular pathologist (M.H.) and two trainees (K.W. and A.G.). Scoring disagreements were adjudicated by the cardiovascular pathologist. Scoring was fairly consistent with generally only minor (1 point) differences needing harmonization across the three reviewers. For example, of the 148 cases, there was >1 point of disagreement on the overall MDS in only 5 cases (3.3%).

2.3. Statistical analysis

All statistical analyses were performed using the statistical programming language R (R Foundation, Vienna, Austria) with a significance level set at .05. Comparisons of median values of histopathologic features between the nonsyndromic and syndromic groups were made using the nonparametric Mann–Whitney *U* test. A Pearson χ^2 test was used to test for differences in the distribution between MEMA types. Spearman tests were used to test for correlation. Multiple regression models adjusting for the syndrome groups were used to assess the association between *Z*-score and number of fragments examined with MDS. A χ^2 test was used to test for differences in the proportion of cases with histologic evidence of atherosclerosis, dissection, foreign body giant cell reaction, vasa vasorum medial thickening, and adventitial fibrosis. We created a multidimensional reduction model of the data in order to examine for clustering using t-Stochastic Neighbor Embedding (t-SNE) using the Rtsne package and perplexity set at 8 (version 0.11) [12]. We included MEMA extent, MEMA severity, EFFL extent, EFFL severity, EFT extent, EFT severity, EFD extent, SMCNL extent, SMNCL severity, LMC severity, SMCD extent, atherosclerosis extent, and adventitial fibrosis extent in our t-SNE model.

Table 1
Demographic and clinical data by syndrome categories

		NS (n=53)	MFS (n=39)	LDS (n=23)	BAV (n=31)	Other (n=2)	All (n=148)
Mean age (S.D.)		63 (15)	30 (14)	20 (16)	50 (11)	40 (40)	45 (22)
Male, *n* (%)		42 (79%)	26 (67%)	15 (65%)	25 (81%)	2 (100%)	110 (74%)
Race, *n* (%)	White	37 (70%)	34 (87%)	17 (74%)	29 (94%)	1 (50%)	118 (80%)
	Black	6 (11%)	4 (10%)	1 (4%)	0 (0%)	0 (0%	11 (8%)
	Hispanic	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
	Asian	4 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (3%)
	Other/Unknown	5 (9%)	1 (3%)	5 (22%)	2 (6%)	1 (50%)	14 (9%)
Surgery indication, *n* (%)	Dissection ± root dilation	21 (40%)	8 (21%)	1 (4%)	0 (0%)	0 (0%)	30 (20%)
	Root dilation w/o dissection	30 (57%)	31 (79%)	22 (96%)	30 (97%)	2 (100%)	115 (78%)
	Other	2 (4%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	3 (2%)
Z-score, mean (S.D.)[a]		4.9 (2.6)	6.5 (2.5)	6.9 (3.2)	5.4 (2.1)	8.0 (4.5)	5.9 (2.7)

[a] Missing data for some patients.