The complex interplay among atherosclerosis, inflammation, and degeneration in ascending thoracic aortic aneurysms

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ABSTRACT

Objective: To assess the histopathological findings of a large series of ascending thoracic aortic aneurysm (TAA) surgical specimens applying the updated classification on noninflammatory degenerative and inflammatory aortic diseases proposed by the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology clinicopathological correlations.

Methods: A total of 255 patients surgically treated for ascending TAA were enrolled. Surgical ascending aorta specimens were examined.

Results: The histopathological substrate of ascending TAAs was mainly degenerative (67.5%), but with a remarkable prevalence of atherosclerotic lesions (18.8%) and aortitis (13.7%). Degenerative patients more frequently had bicuspid aortic valve (37.2%; $P = .002$). Patients in the atherosclerotic group were older (median age, 69 years; $P < .001$), more often with a history of hypertension (87.5%; $P = .059$), hypercholesterolemia (75%; $P = .019$), diabetes (16.6%; $P = .054$), current smoking (22.9%; $P = .066$), and a history of coronary artery disease (18.7%; $P = .063$). Patients with aortitis represented the older group (median age, 75 years, $P < .001$), were mostly females (68.6%; $P < .001$), and had a larger ascending aorta diameter (median, 56 mm; $P < .001$). Both patients with atherosclerosis and aortitis presented a higher incidence of concomitant abdominal aortic aneurysm (20.8% and 22.8%, respectively; $P < .001$).

Conclusions: Although degenerative histopathology is the most frequent substrate in ascending TAA, atherosclerosis and inflammation significantly contribute to the development of chronic aortic thoracic disease. (J Thorac Cardiovasc Surg 2019;■:1-10)
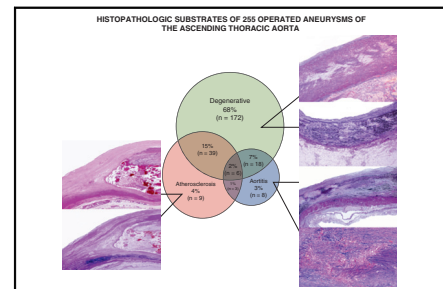
Histopathologic substrates of 255 operated aneurysms of the ascending thoracic aorta.

Central Message

Degenerative histopathology is the most frequent substrate in ascending thoracic aortic aneurysms, but atherosclerosis and inflammation contribute significantly to the development of chronic aortic thoracic disease.

Perspective

Awareness of the significant burden of aortitis and atherosclerosis-related inflammation might guide future research and therapies in the field of ascending thoracic aortic aneurysms.

See Commentary on page XXX.

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From a clinical standpoint, thoracic aortic diseases mainly include thoracic aortic aneurysm (TAA) and type A acute aortic syndromes (AAS), which include aortic dissection, intramural hematoma, and penetrating aortic ulcer. Previous histopathological studies in chronic thoracic aortic diseases have focused mainly on the role of degenerative lesions of the medial aortic layer, first identified by Erdheim in 1930

Scanning this QR code will take you to the article title page to access supplementary information.

Abbreviations and Acronyms
AAS	= acute aortic syndrome
AECVP	= Association for European Cardiovascular Pathology
AHA	= American Heart Association
BAV	= bicuspid aortic valve
CAD	= coronary artery disease
EFFL	= elastic fiber fragmentation/loss
EFTO	= elastic fiber thinning out
ICI	= intralamellar collagen increase
I-MEMA	= intralamellar mucoid extracellular matrix accumulation
LMC	= laminar medial collapse
MD	= medial degeneration
SCVP	= Society for Cardiovascular Pathology
TAA	= thoracic aortic aneurysm
TCI	= translamellar collagen increase
T-MEMA	= translamellar mucoid extracellular matrix accumulation

as "aortic idiopathic (cystic) medial necrosis,"[1] leading to the common perception of TAA as a mainly genetic-based disease associated with degenerative substrate. This conception may be challenged by recent histopathological advances, however. In particular, the Association for European Cardiovascular Pathology (AECVP) and the Society for Cardiovascular Pathology (SCVP) have proposed a revised and updated classification of the histopathologic diagnostic criteria for aortic diseases in 2 consensus statements on noninflammatory-degenerative[2] and inflammatory[3] aortic diseases. These criteria have not been applied to a large ascending TAA series to date.

In the present study, we assessed the histopathological findings of a large series of ascending TAA surgical specimens and searched for clinicopathological correlations.

METHODS

Clinical Setting and Study Design

The study population consisted of 255 patients who underwent surgery for ascending TAA at our center between January 1, 2015, and December 31, 2016. Patients age <18 years were excluded. We compared histopathological profiles of patients with chronic ascending TAA with those of patients with a final diagnosis of spontaneous type A acute aortic syndrome (AAS) treated surgically at our center between January 1, 2000, and December 31, 2013, whose data have been previously reported by our group.[4] The study conforms to the principles outlined in the Declaration of Helsinki and was approved by our institutional Ethics Committee.

Clinical Definitions

The study population's main characteristics and clinical features at presentation were evaluated. Cardiovascular risk factors included a history of hypertension and ongoing antihypertensive therapy, hypercholesterolemia (total cholesterol >200 mg/dL) and ongoing lipid-lowering therapy, diabetes (type 1 or type 2), current smoking, familial history of premature

coronary artery disease (CAD; ie, history of myocardial infarction affecting a first-degree relative younger than 55 years if men and 65 years if women). Known TAA in patients operated on for ascending TAA was defined as the presence of aneurysm in another thoracic vascular segment. Baseline glomerular filtration rate was calculated using the modified Modification of Diet in Renal Disease Study equation.[5]

Histopathology

Ascending aorta specimens ranging in length from 2.5 to 4.5 cm were examined for patients undergoing surgery for ascending TAA. An average of 6 samples were taken from each formalin-fixed specimen, processed routinely, and embedded in paraffin. The histologic sections were stained with standard hematoxylin and eosin and histomorphological staining for collagen (Azan-Mallory trichrome) and elastic fibers (Weigert-Van Gieson staining).

Histological samples were all evaluated de novo according to the diagnostic criteria from the 2 AECVP/SCVP documents[2,3] by personnel blinded to the clinical data. Specifically, 2 categories of abnormalities were evaluated: noninflammatory/degenerative substrates and inflammatory substrates.

Noninflammatory/degenerative substrates. Overall degeneration of the aortic media was assessed as the sum of 6 major individual lesions involving various cellular and extracellular components of the medial layer:

- Mucoid extracellular matrix accumulation, an increase of mucopolysaccharides, both intralamellar (I-MEMA), preserving the arrangement of lamellar unit, and translamellar (T-MEMA), altering the structural architecture of the tunica media due to large pool formation
- Elastic fiber fragmentation/loss (EFFL)
- Elastic fiber thinning out (EFTO)
- Laminar medial collapse (LMC), a thin/dense band-like smooth muscle cell loss generating architectural compaction of elastic fibers
- Collagen increase, intralamellar (ICI), in the absence of significant alterations of the lamellar unit, and translamellar (TCI; ie, replacement fibrosis).

Overall medial degeneration (MD) was graded as mild, moderate, or severe, based on severity and distribution of each individual abnormality.

Inflammatory substrates.

- Atherosclerosis. After assessing single atherosclerotic plaques using the American Heart Association (AHA) schemes,[6,7] atherosclerosis was classified and graded as not significant, mild, moderate, or severe using the simplified AECVP/SCVP classification, according to which only moderate or severe disease leads to significant medial damage
- Atherosclerosis with excessive inflammation (ie, with intense inflammatory reaction)
- Inflammatory atherosclerotic aneurysm
- Aortitis and periaortitis, classified according to histopathological inflammatory patterns (granulomatous/giant cells, lymphoplasmacytic, mixed inflammatory, and suppurative).

Only patients with moderate to severe atherosclerotic disease (AHA plaques V-VII) were classed as atherosclerotic.

Clinicopathological Correlations

To investigate clinicopathological correlations, the patients were classified according to 3 histopathological patterns: isolated degeneration (pure degenerative lesions or associated with mild atherosclerosis, ie AHA plaques I-IV), mainly atherosclerosis in the presence of moderate to severe atherosclerosis (isolated or associated with various degrees of degeneration), and aortitis (isolated or associated with various degrees of MD or atherosclerosis).

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Statistical Analysis

Categorical variables are expressed as number and percentage. Continuous variables are expressed as mean ± standard deviation or median and interquartile range for normal or non-normal distribution, respectively.

Comparisons between categorical variables were performed with the χ^2 test. Comparisons between 2 continuous variables were performed with the Student t test or Wilcoxon test as appropriate. Comparisons among 3 groups were performed with analysis of variance (ANOVA) for height values and the Kruskal-Wallis test when the assumptions for ANOVA application were not met (ie, age, body mass index, glomerular filtration rate, systolic and diastolic blood pressure values, and ascending aorta diameters).

Variables with $P < .1$ in the univariate analysis were included in the multivariable analysis (multinomial logit model). All statistical analyses were performed using STATA/SE 14.2 (StataCorp, College Station, Tex).

RESULTS

Clinical Findings in Patients With Ascending TAA

Severe aortic stenosis was present in 26 of the 255 patients; severe aortic regurgitation in 77 patients, and concomitant severe stenosis and regurgitation in 4 patients. Concomitant aortic valve replacement was performed in 196 of the 255 patients.

Indications for surgery were as follows: maximal ascending aorta diameter ≥55 mm in 117 patients, maximal ascending aorta diameter ≥50 mm in the presence of a bicuspid aortic valve with additional risk factors in 29 patients, maximal ascending aorta diameter ≥45 mm in the presence of Marfan syndrome in 5 patients and Loeys-Dietz syndrome in 1 patient, and severe aortic stenosis or regurgitation with maximal ascending aorta diameter ≥45 mm in 103 patients. Table 1 reports the baseline characteristics and clinical features of the 255 patients with ascending TAA.

The median patient age was 66 years. A history of hypertension and antihypertensive therapy was common (n = 211; 82.7%), as were hypercholesterolemia (n = 134; 52.5%) and receipt of lipid-lowering therapy (n = 81; 31.7%). A higher percentage of patients were ex-smokers compared with current smokers (32.9% [n = 84] vs 13.7% [n = 35]).

Bicuspid aortic valve (BAV) was common in patients with ascending TAA (n = 77; 30.1%), whereas Marfan syndrome was rare (n = 5; 1.9%); patients with BAV were younger (58 years vs 69 years; $P < .001$), and a had a lower rate of hypertension (74% [n = 57] vs 86.5% [n = 154]; $P = .015$) (Table E1). The incidence of concomitant abdominal aortic aneurysm was 10.5% (n = 27).

Histopathological Findings in Patients With Ascending TAA

Tables 2 and E2 and Figures 1 and 3 present histopathological findings. In approximately 75% of the patients with ascending TAA, histopathology revealed a single pattern

TABLE 1. Characteristics of the Study Population at Presentation (N = 255)

Characteristic	Value
Age, y, median (IQR)	66 (58-74)
Male sex, n (%)	189 (74.1)
BMI, kg/m², median (IQR)	26 (24-28)
Height, cm, mean ± SD	171 ± 10
Hypertension history, n (%)	211 (82.7)
Antihypertensive therapy, n (%)	211 (82.7)
Hypercholesterolemia, n (%)*	134 (52.5)
Lipid-lowering therapy, n (%)	81 (31.7)
Diabetes, n (%)	21 (8.2)
Insulin-dependent diabetes, n (%)	16 (6.2)
Non–insulin-dependent diabetes, n (%)	5 (1.9)
Current smoker, n (%)	35 (13.7)
Ex-smoker, n (%)	84 (32.9)
Familial history of CAD, n (%)	48 (18.8)
Previous ACS/exertion-induced angina, n (%)	25 (9.8)
Previous PTCA or CABG, n (%)	29 (11.3)
PAOD, n (%)	1 (0.3)
Previous stroke/TIA, n (%)	15 (5.8)
Clinical diagnosis of aortitis, n (%)	5 (1.9)
Aortic coarctation, n (%)	3 (1.1)
Bicuspid aortic valve, n (%)	77 (30.1)
Turner syndrome, n (%)	1 (0.3)
Marfan syndrome, n (%)†	5 (1.9)
Loeys-Dietz syndrome, n (%)†	1 (0.3)
Ehlers-Danlos syndrome, n (%)†	0 (0)
Previous aortic surgery, n (%)	20 (7.8)
Previous AAS, n (%)	7 (2.7)
Known thoracic aortic aneurysm (surgically treated or not), n (%)‡	13 (5.1)
Known abdominal aortic aneurysm (surgically treated or not), n (%)	27 (10.5)
Familial history of aortic disease, n (%)	15 (5.8)
GFR, mL/min/1.73 m², median (IQR)	84 (66-102)
Systolic blood pressure (mm Hg), median (IQR)	120 (120-135)
Diastolic blood pressure (mm Hg), median (IQR)	80 (70-80)
Maximum ascending aorta diameter (mm), median (IQR)§	51 (47-55)

IQR, Interquartile range; *BMI*, body mass index; *SD*, standard deviation; *CAD*, coronary artery disease; *ACS*, acute coronary syndrome; *PTCA*, percutaneous transluminal coronary angioplasty; *CABG*, coronary artery bypass graft; *PAOD*, peripheral arterial occlusive disease; *TIA*, transient ischemic attack; *AAS*, acute aortic syndrome; *GFR*, glomerular filtration rate. *When the total cholesterol value was >200 or when the patient received lipid-lowering therapy. †A systematic genotyping was not available, so the effective prevalence of the different genetic syndromes could have been underestimated in our study population. ‡Aneurysm in a thoracic aortic segment other than ascending. §Data available for 253 of 255 patients.

TABLE 2. Histopathological findings in the study population (N = 255)

Diagnostic group	Value, n (%)
Inflammatory-atherosclerosis	9 (3.5)
Inflammatory-aortitis	8 (3.1)
Degenerative	172 (67.5)
Mixed: Degenerative-atherosclerosis	39 (15.2)
Mixed: Degenerative-aortitis	18 (7.1)
Mixed: Atherosclerosis-aortitis	3 (1.1)
Mixed: Degenerative-atherosclerosis-aortitis	6 (2.3)

(degenerative in 67.5% of cases, atherosclerosis in 3.5%, and aortitis in 3.1%), whereas in approximately 25%, the pattern was mixed (degenerative-atherosclerosis in 15.2%, degenerative-aortitis in 7.1%, atherosclerosis-aortitis in 1.1%, and degenerative-atherosclerosis-aortitis in 2.3%).

When the patients with ascending TAA were classified according to the 3 main histopathological patterns, MD was present in 172 (67.5%), mainly atherosclerosis in 48 (18.8%), and aortitis in 35 (13.7%).

MD was the most frequent histopathological substrate found in ascending TAA (n = 235; 92.2%), with isolated (n = 172; 67.5%) or mixed patterns (n = 63; 24.6%) and was most frequently moderate (n = 130; 50.9%). As to individual degenerative lesions, MEMA was the most frequent type (n = 244; 95.6%), more T-MEMA (n = 234; 91.7%) than I-MEMA (n = 201; 78.8%), followed by EFFL (n = 243; 95.2%), ICI (n = 219; 85.8%), and EFTO (n = 201; 78.8%). TCI and LMC were relatively rare (n = 92 [36%] and n = 68 [26.6%], respectively), the latter being more frequently associated with atherosclerosis rather than with a degenerative substrate. In particular, LMC associated with atherosclerosis was represented by a thick compaction band bordering the medial side of the plaques (Figure 1). Mucoid extracellular matrix and elastic fiber lesions, as well as ICI, were more frequently moderate and multifocal.

Atherosclerosis was present in a significant number of patients (n = 57; 22.3%), most prevalently as a mixed pattern (degenerative-atherosclerosis in 39 [15.2%], atherosclerosis-aortitis in 3 [1.1%], and degenerative-atherosclerosis-aortitis in 6 [2.3%]). Atherosclerosis was graded moderate in 29 patients (10.9%) and severe in 29 patients (11.3%). In 81 patients (31.7%), atherosclerotic lesions were mild and associated with other histopathological patterns. Atherosclerosis with excessive inflammation and inflammatory atherosclerotic aneurysm were very rare, found in 1 patient with ascending TAA (Figure 1).

Aortitis was found in 35 patients (13.7%), most prevalently with a granulomatous-giant cell pattern (n = 20;

7.8%), followed by lymphoplasmacytic (n = 2; 0.7%). In 5.1% of cases (13 patients), the inflammatory process was in a chronic/healing phase, the aortitis pattern was difficult to classify, and aortitis was considered unclassified; the inflammatory cell types were described, as was the presence of necrosis and scarring (Figure 1). All aortic specimens with aortitis had severely damaged vessel walls.

Periaortitis was present in 28 of 35 cases of ascending TAA aortitis (80%) and was also found in other 17 cases of ascending TAA, where the histopathological substrate was atherosclerotic or degenerative (Figure 1). The periaortic inflammatory infiltrate grading was more frequently moderate (n = 26; 10.1%) than mild (n = 10; 3.9%) or severe (n = 9; 3.5%).

Clinicopathological Correlations in Patients With Ascending TAA

As shown in Table 3 and Figure 2, the clinicopathological correlations were assessed according to 3 main categories: isolated degeneration (n = 172; 67.5%), mainly atherosclerosis (n = 48; 18.8%) and aortitis (35, 13.7%). The patients with isolated degeneration more frequently had a bicuspid aortic valve. The patients in the mainly atherosclerosis group were older and more often had a history of hypertension, hypercholesterolemia, diabetes, current smoking, and CAD, particularly compared with the isolated degeneration group. The aortitis group was the oldest group, had a female predominance, and had a high prevalence of classical cardiovascular risk factors, such as hypertension, hypercholesterolemia, and diabetes. Moreover, a larger ascending aorta was more prevalent in the atherosclerotic group and even more so in the aortitis group. The prevalence of concomitant abdominal aortic aneurysm was higher in the atherosclerosis and aortitis groups compared with the isolated degeneration group. After multivariable analysis, variables independently associated with atherosclerotic patterns were older age, higher BMI, hypercholesterolemia, smoking, and larger ascending aorta diameter, and variables independently associated with aortitis pattern were older age, female sex, higher BMI, and larger ascending aorta diameter (Table 4).

The distribution of histopathological lesions according to age in ascending TAA patients is reported in Table E3. Degenerative lesions were more frequent in patients age ≤65 years (n = 118; 46.3%) compared with those age >65 years (n = 137; 53.7%) (n = 99 [83.8%] vs n = 73 [53.2%]; P < .001) than. In contrast, older patients more frequently had mixed degenerative-atherosclerotic lesions were more common in the patients age >65 years (n = 29 [21.1%] vs n = 10 [8.4%]; P = .008). Overall MD grading was similar in the 2 age groups. As to individual degenerative lesions, the younger patients had more intralamellar MEMA, EFTO and ICI, whereas the older ones had more TCI. No between-group differences were found in EFFL
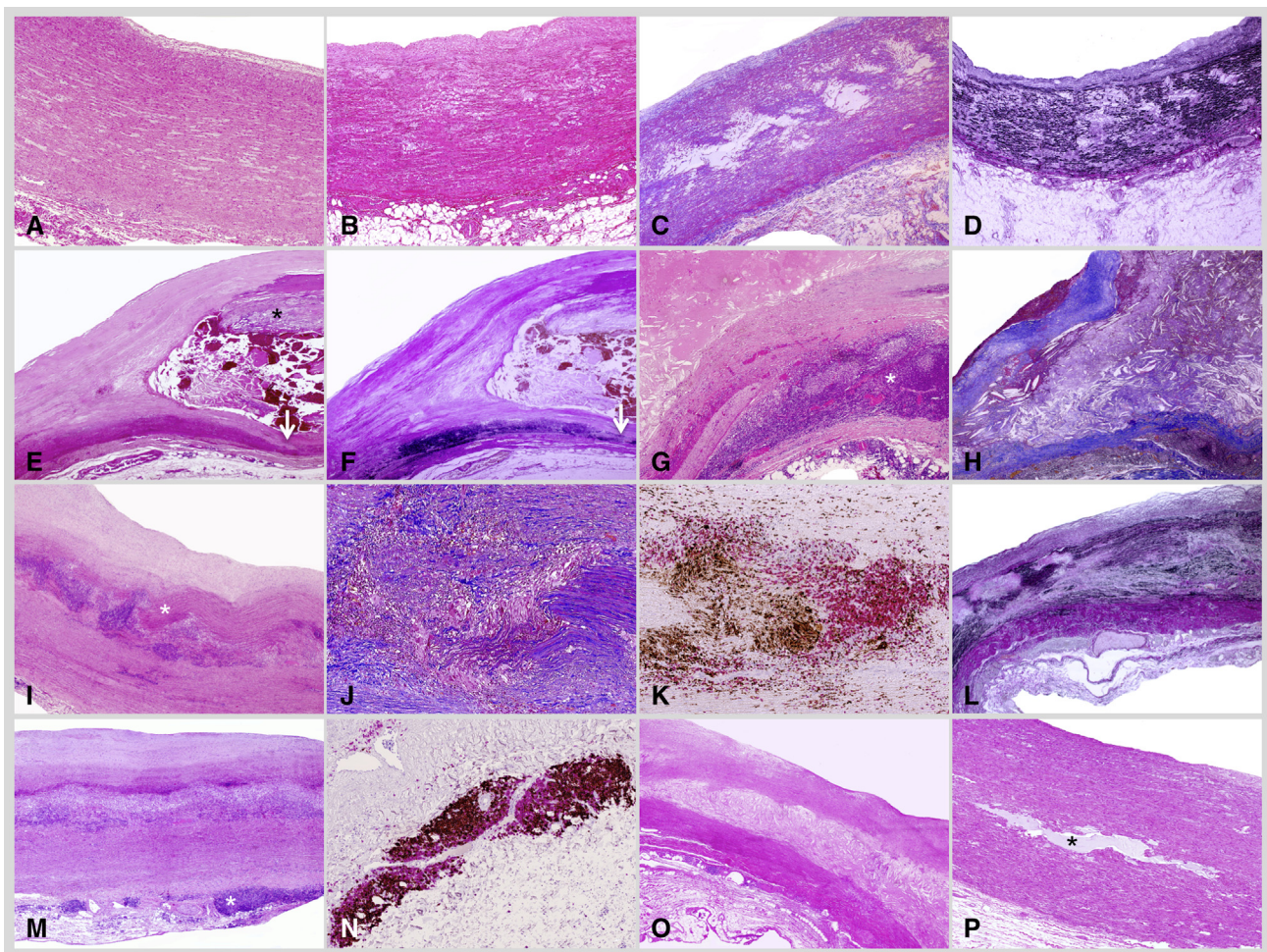
FIGURE 1. Main histopathologies of ascending thoracic aortic aneurysm. A-D, Degenerative aneurysm cases. A, Mild medial degeneration (MD) prevalently characterized by elastic fiber thinning out (EFTO) and intralamellar mucoid extracellular matrix accumulation (I-MEMA) (hematoxylin and eosin, 50×). B, Moderate degenerative alterations with EFTO/elastic fiber fragmentation/loss (EFFL) and I-MEMA/translamellar mucoid extracellular matrix accumulation (T-MEMA) (hematoxylin and eosin, 50×). C and D, Severe MD with large areas of accumulated extracellular matrix (C, Azan-Mallory trichrome stain, 25×) and severe EFFL (D, Weigert-Van Gieson stain, 25×). E-H, Mainly atherosclerosis pattern. E and F, Advanced fibroatheroma with calcification (*asterisk*). The underlying medial layer is thinned and destroyed by replacement fibrosis (E, *arrow*; hematoxylin and eosin; 25×); only residual elastic lamellas are evident (F, *arrow*; Weigert-Van Gieson stain; 25×). G and H, Inflamed atherosclerosis with plaque rupture. Under the plaque and in the periaortic tissue are extensive inflammatory infiltrates, partially with a follicular-like structure (G, *asterisk*, hematoxylin and eosin, 25×; H, Azan-Mallory trichrome stain, 25×). I-L, Giant cell aortitis, the most frequent type found. I, Severe and extensive inflammation in the medial layer and at the intimal-medial junction associated with areas of acellular laminar necrosis (*asterisk*, hematoxylin and eosin, 25×). J, Inflammatory infiltrates are composed of lymphocytes, macrophages, and giant cells with or without granulomas (Azan-Mallory trichrome stain, 50×). K, Double CD68/CD3 immunostaining highlights macrophages and giant cells (*brown*) and T lymphocytes (*red*) (original magnification 100×). L, Elastic fiber staining highlighting the severe, widespread alteration of the aortic wall due to the inflammatory disease (Weigert-Van Gieson stain, 25×). M-P, A case of severe aortitis with granulomatous/giant cell pattern and chronic periaortitis (M, *asterisk*, hematoxylin and eosin, 25×). N, Double CD20/CD3 immunostaining showing that B lymphocytes (*brown*) prevail over T lymphocytes (*red*) (original magnification, 100×). O and P, Aneurysm with mixed atherosclerosis-degenerative pattern: fibroatheroma (American Heart Association grade V) (hematoxylin and eosin, 25×) and, in another area, extracellular matrix accumulation (T-MEMA) within an EFFL zone (hematoxylin and eosin, 25×).

and translamellar MEMA. The grading of atherosclerosis was more frequently severe in the older patients (n = 24 [17.5%] vs n = 5 [4.2%]; $P = .001$). Aortitis was more frequent in the older patients (n = 29 [21.1%] vs n = 6 [5.1%]; $P < .001$), with a pattern that was predominantly granulomatous-giant cell and healed.

DISCUSSION

Here we report the histopathological findings of a large series of patients with TAA using the recent and not yet widely validated AECVP and SCVP classification systems.[2,3] This new system is receiving increasing attention for many reasons, including the standardization of
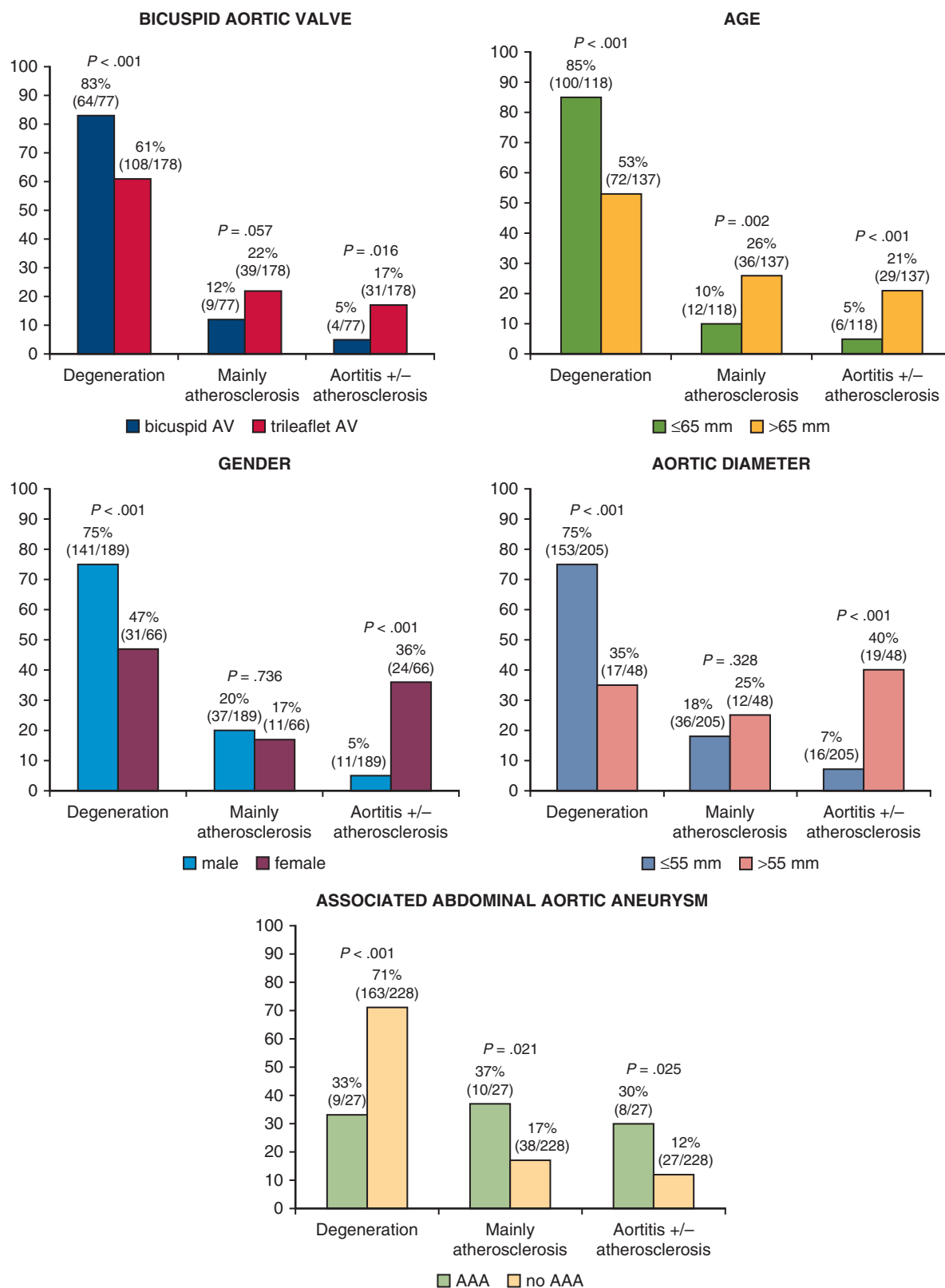
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FIGURE 2. Histopathological findings according to predefined subgroups in patients with ascending thoracic aortic aneurysm. *AV*, Aortic valve; *AAA*, abdominal aortic aneurysm.

HISTOPATHOLOGIC SUBSTRATES OF 255 OPERATED ANEURYSMS OF THE ASCENDING THORACIC AORTA
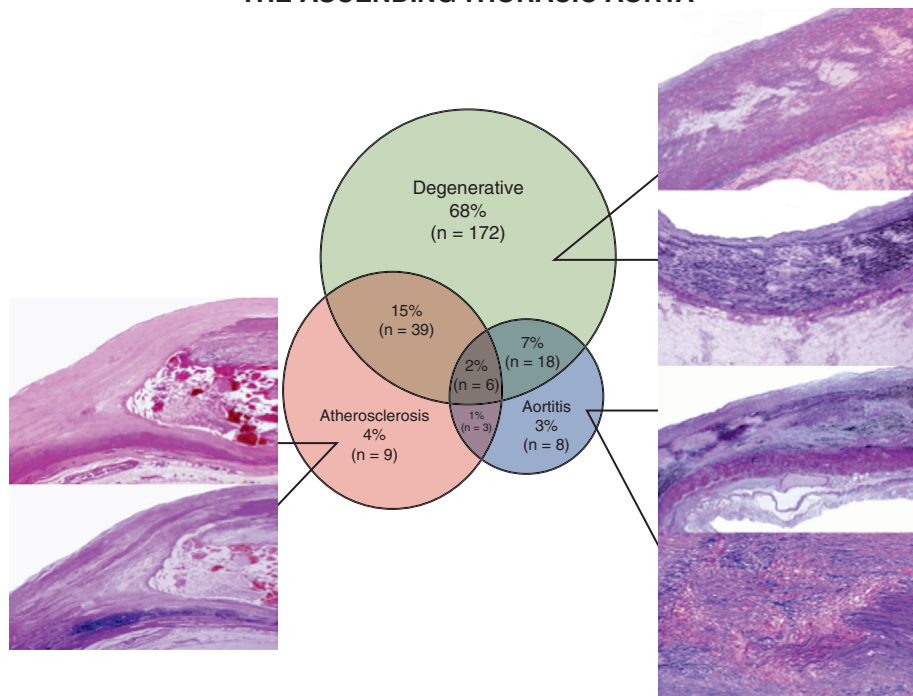

FIGURE 3. The spectrum of histopathological findings in patients with ascending thoracic aortic aneurysm.

nomenclature, a clear definition of diagnostic categories, and the standardization of histopathological diagnostic criteria for inflammatory and degenerative lesions, still a poorly defined topic. Our study documents the applicability and usefulness of such a system in the setting of ascending aorta lesions necessitating surgical therapy.

Although MD is confirmed as the most common finding in ascending TAA,[8] atherosclerosis and aortitis are the main histopathological substrates in a significant number of cases (1 in 3). Across these main patterns, mixed forms (with 2 or more types of lesions) are quite common (approximately 25%).

Comparing the histopathological profile of patients with ascending TAA with that seen in a series of patients operated on for type A AAS previously described by our group,[4] we see that acute and chronic forms have a similar prevalence of degenerative and atherosclerotic lesions (in AAS, isolated MD in 77.2% and mainly atherosclerosis in 22.8%). In both ascending TAA and AAS, the coexistence of 2 or more patterns (mixed forms) is also quite common (approximately 25%). Of note, the presence of LMC is not confined to the degenerative pattern but can also be associated with atherosclerosis and is likely the common final result of different pathogenetic mechanisms; LMC is much more frequent and extensive in the acute setting. Patients with AAS showed a higher prevalence of severe MD lesions compared with those with

ascending TAA (24.1% vs 14.9%), and aortitis was found in 13.7% of ascending TAA cases but was not described in the AAS setting.

Our study also provides some interesting clinicopathological correlations by comparing clinical profiles across the 3 main histological patterns (Table 3) and considering 5 prespecified subgroups (Figure 2). Compared with degenerative patients, atherosclerotic patients with ascending TAA were older and more frequently had a history of hypertension, hypercholesterolemia, diabetes, current smoking, and a history of coronary artery disease. Patients with aortitis were older and mostly female, and had significantly larger ascending aortas. Similar correlations among sex, age, and histological substrate of aortic lesions have been reported by Nesi and colleagues[8] in a cohort of 171 patients with surgically treated TAA. In patients with aortitis, the most common histopathological pattern was granulomatous-giant cell, as reported in other series.[9,10] Approximately 40% of patients with aortitis showed a healing phase, with massive fibrosis likely protecting the wall from dissection. Chronic periaortitis was associated with 80% of cases and likely contributed to the overall remodeling process. In most cases, the diagnosis of aortitis had not been suspected before surgery. Aortic and periaortic inflammation can be investigated with noninvasive imaging techniques, but the therapeutic implications remain to be been fully established.[11]

TABLE 3. Clinicopathological correlations in patients with thoracic aortic aneurysm

Characteristic	Isolated degeneration (N = 172; 67.5%)	Mainly atherosclerosis (N = 48; 18.8%)	Aortitis with/without atherosclerosis (N = 35; 13.7%)	P value
Age, y, median (IQR)	63 (53-70)	69 (66-75)	75 (71-78)	<.001
Male sex, n (%)	141 (81.9)	37 (77.1)	11 (31.4)	<.001
BMI, kg/m^2, median (IQR)	26 (24-28)	27 (24-30)	27 (24-30)	.12
Height, cm, mean ± SD	173 ± 9	171 ± 10	163 ± 10	.808
Hypertension (history), n (%)	136 (79.1)	42 (87.5)	33 (94.2)	.059
Antihypertensive therapy, n (%)	137 (79.6)	41 (85.4)	33 (94.2)	.097
Hypercholesterolemia, n (%)*	90 (52.3)	36 (75)	20 (57.1)	.019
Lipid-lowering therapy, n (%)	40 (23.2)	30 (62.5)	11 (31.4)	<.001
Diabetes, n (%)	10 (5.8)	8 (16.6)	3 (8.5)	.054
Insulin-dependent diabetes, n (%)	3 (1.7)	2 (4.1)	0 (0)	.376
Non–insulin-dependent diabetes, n (%)	7 (4)	6 (12.5)	3 (8.5)	.086
Current smoker, n (%)	22 (12.7)	11 (22.9)	2 (5.7)	.066
Ex-smoker, n (%)	49 (28.4)	21 (43.7)	14 (40)	.088
Familial history of CAD, n (%)	32 (18.6)	12 (25)	3 (8.5)	.162
Previous ACS/exertion-induced angina, n (%)	14 (8.1)	9 (18.7)	2 (5.7)	.063
Previous PTCA or CABG, n (%)	18 (10.4)	8 (16.6)	3 (8.5)	.417
PAOD, n (%)	1 (0.5)	0 (0)	0 (0)	.785
Previous stroke/TIA, n (%)	9 (5.2)	3 (6.2)	3 (8.5)	.741
Clinical diagnosis of aortitis, n (%)	0 (0)	1 (2.1)	4 (11.4)	<.001
Aortic coarctation, n (%)	3 (1.7)	0 (0)	0 (0)	.481
Bicuspid aortic valve, n (%)	64 (37.2)	9 (18.7)	4 (11.4)	.002
Turner syndrome, n (%)	1 (0.5)	0 (0)	0 (0)	.785
Marfan syndrome, n (%)	5 (2.9)	0 (0)	0 (0)	.292
Loeys-Dietz syndrome, n (%)	1 (0.5)	0 (0)	0 (0)	.785
Ehlers-Danlos syndrome, n (%)	0 (0)	0 (0)	0 (0)	NA
Previous aortic surgery, n (%)	13 (7.5)	6 (12.5)	1 (2.8)	.264
Previous AAS, n (%)	6 (3.4)	1 (2.1)	0 (0)	.491
Known thoracic aortic aneurysm (surgically treated or not), n (%)†	6 (3.4)	5 (10.4)	2 (5.7)	.153
Known abdominal aortic aneurysm (surgically treated or not), n (%)	9 (5.2)	10 (20.8)	8 (22.8)	<.001
Familial history of aortic disease, n (%)	11 (6.3)	3 (6.2)	0 (0)	.308
GFR, mL/min/1.73 m^2, median (IQR)	88 (73-103)	79 (64-94)	66 (55-88)	.471
Systolic blood pressure (mm Hg), median (IQR)	120 (120-130)	120 (120-140)	120 (120-140)	.219
Diastolic blood pressure (mm Hg), median (IQR)	80 (70-80)	80 (75-80)	80 (70-80)	.271
Maximum ascending aorta diameter (mm), median (IQR)	50 (46-53)‡	52 (50-58)	56 (51-62)	<.001

IQR, Interquartile range; *BMI*, body mass index; *SD*, standard deviation; *CAD*, coronary artery disease; *ACS*, acute coronary syndrome; *PTCA*, percutaneous transluminal coronary angioplasty; *CABG*, coronary artery bypass graft; *PAOD*, peripheral arterial occlusive disease; *TIA*, transient ischemic attack; *NA*, not applicable; *AAS*, acute aortic syndrome; *GFR*, glomerular filtration rate. *When the total cholesterol value was >200 or when the patient received lipid-lowering therapy. †Aneurysm in a thoracic aortic segment other than ascending. ‡Data available for 170 of 172 patients.

Patients with ascending TAA with atherosclerosis and aortitis frequently had a concomitant abdominal aortic aneurysm. The pathogenetic role of inflammation in aortic aneurysms has been addressed mainly in the context of abdominal aneurysms,[12-17] whereas the implications of inflammatory substrates for thoracic aortic remodeling have yet to be fully established.[12,18,19] Medial inflammatory response to atherosclerosis is known to correlate with a negative histological remodeling of the aortic media.[20]

TABLE 4. Multivariable analysis for clinicopathological correlations in patients with thoracic aortic aneurysm

Variable	Mainly atherosclerosis vs isolated degeneration, OR (95% CI)	P value	Aortitis with/without atherosclerosis vs isolated degeneration, OR (95% CI)	P value	Mainly atherosclerosis vs aortitis with/without atherosclerosis, OR (95% CI)	P value
Age (for each 1-y increase)	1.08 (1.03-1.13)	.002	1.09 (1.03-1.17)	.004	1.01 (0.95-1.09)	.676
Male sex	0.45 (0.17-1.23)	.123	0.05 (0.01-0.15)	<.001	0.11 (0.04-0.34)	<.001
BMI (for each 1 kg/m^2 increase)	1.11 (1-1.23)	.034	1.15 (1.01-1.3)	.03	1.03 (0.91-1.17)	.64
Hypertension (history)	0.61 (0.16-2.24)	.461	2.83 (0.42-18.94)	.282	4.61 (0.62-34.5)	.136
Hypercholesterolemia*	2.92 (1.2-7.12)	.018	1.36 (0.49-3.73)	.544	0.47 (0.15-1.44)	.184
Diabetes	2.35 (0.75-7.32)	.139	1.31 (0.24-7.16)	.75	0.56 (0.1-0.05)	.502
Current smoker	3.95 (1.32-11.76)	.014	0.71 (0.11-4.5)	.717	0.17 (0.03-1.16)	.072
Ex-smoker	3.18 (1.32-7.62)	.009	2.23 (0.74-6.69)	.151	0.7 (0.22-2.23)	.55
Previous ACS/exertion-induced angina	1.23 (0.39-3.82)	.715	0.48 (0.07-3.07)	.446	0.39 (0.06-2.57)	.333
Bicuspid aortic valve	0.94 (0.35-2.49)	.904	0.66 (0.16-2.73)	.576	0.71 (0.15-3.31)	.664
Known abdominal aortic aneurysm (surgically treated or not)	1.14 (0.34-3.73)	.825	1.58 (0.38-6.51)	.523	1.38 (0.34-5.68)	.649
Maximum ascending aorta diameter (for each 1-mm increase)	1.08 (1.03-1.14)	.001	1.08 (1.02-1.15)	.005	0.99 (0.95-1.04)	.895

OR, Odds ratio; *CI*, confidence interval; *BMI*: body mass index; *ACS*: acute coronary syndrome. *When the total cholesterol value was >200 or when the patient received lipid-lowering therapy.

Overall, age was a strong determinant of the histopathological substrate, with a higher prevalence of atherosclerosis and aortitis in subjects age >65 years (Figure 2). Age also influences the type of degenerative lesion. Age-related aortic changes include the loss of elastin content with elastic fiber fragmentation and loss and increase of other matrix components, primarily collagen. Fragmentation of elastic fibers creates gaps in the lamellar structure of the aorta, which are partially filled with proteoglycans (T-MEMA). In our cohort, younger patients were found to have I-MEMA and EFTO more frequently, whereas the prevalences of EFFL and T-MEMA were similar in the 2 age groups. Increased collagen was more frequently intralamellar in young patients and translamellar in older ones, where the scar-like morphology suggests a repair process.

It was difficult to assess the effect of genetics on the histological substrate in our cohort, due to the low prevalence of patients with genetic syndromes and the unavailability of systematic genotyping. Nonetheless, it is known that genetic syndromes lead to degenerative changes that are mainly mucoid, and that elastic fiber lesions are more extensive and occur at an earlier age.[21] A recent study by Waters and colleagues[22] that analyzed 148 surgical ascending aorta specimens (including both aneurysms and dissections) found that patients with Marfan syndrome had more overall MD and MEMA compared with patients with other hereditary syndromes and those with nonsyndromic aortopathies. In our study population, the 5 patients with Marfan syndrome were younger (mean age, 37 years) with a purely degenerative substrate and overall moderate MD in 3 cases and severe MD in 2 cases.

BAV was associated with MD lesions in approximately 83% of cases. BAV was frequent in patients with ascending TAA and relatively rare in our previously described series of AAS, but this is at least partially due to our center's policy of prophylactic surgery in patients with BAV and aortic dilatation.

This study has several limitations. We analyzed a single-center cohort with a limited number of patients and without systematic genetic assessment. The possible prognostic implications of histological findings in this setting were not assessed. The exclusion of patients age <18 necessarily restricted the spectrum of histopathological findings and the contribution of genetic-based mechanisms.

CONCLUSIONS

Although degenerative histopathology is the most frequent substrate in ascending TAA, atherosclerosis and inflammation significantly contribute to the development of chronic aortic thoracic disease, either in isolation or in mixed patterns. Awareness of the significant burden of aortitis and atherosclerosis-related inflammation could potentially guide future research and the development of innovative therapies in this field.

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Key Words: aortic aneurysm, aortitis, atherosclerosis, aortic media degeneration, cardiac surgery

TABLE E1. Clinical findings in patients with or without bicuspid aortic valve

Characteristic	Bicuspid aortic valve (N = 77; 30.2%)	Tricuspid aortic valve (N = 178; 69.8%)	P value
Age, y, median (IQR)	58 (49-67)	69 (62-75)	<.001
Male sex, n (%)	58 (75.3)	131 (73.5)	.772
BMI, kg/m^2, median (IQR)	25 (23-29)	26 (24-28)	.546
Height, cm, mean $\pm$ SD	174 $\pm$ 9	170 $\pm$ 10	.997
Hypertension (history), n (%)	57 (74)	154 (86.5)	.015
Antihypertensive therapy, n (%)	56 (72.7)	155 (87.1)	.005
Hypercholesterolemia, n (%)*	29 (37.6)	81 (45.5)	.217
Lipid-lowering therapy, n (%)	20 (25.9)	61 (34.2)	.191
Diabetes, n (%)	8 (10.3)	13 (7.3)	.458
Insulin-dependent diabetes, n (%)	7 (9.1)	9 (5.1)	.262
Non–insulin-dependent diabetes, n (%)	1 (1.2)	4 (2.2)	.992
Current smoker, n (%)	10 (12.9)	25 (14)	.978
Ex-smoker, n (%)	19 (24.6)	65 (36.5)	.081
Familial history of CAD, n (%)	12 (15.5)	35 (19.6)	.441
Previous ACS/exertion-induced angina, n (%)	8 (10.3)	17 (9.6)	.836
Previous PTCA or CABG, n (%)	5 (6.5)	24 (13.4)	.161
PAOD, n (%)	0 (0)	1 (0.5)	.51
Previous stroke/TIA, n (%)	2 (2.6)	13 (7.3)	.143
Clinical diagnosis of aortitis, n (%)	1 (1.3)	4 (2.2)	.616
Aortic coarctation, n (%)	2 (2.5)	1 (0.5)	.166
Marfan syndrome, n (%)	1 (1.3)	4 (2.2)	.616
Turner syndrome, n (%)	0 (0)	1 (0.5)	.51
Loeys-Dietz syndrome, n (%)	0 (0)	1 (0.5)	.51
Ehlers-Danlos syndrome, n (%)	0 (0)	0 (0)	NA
Previous aortic surgery, n (%)	4 (5.2)	16 (8.9)	.301
Previous AAS, n (%)	0 (0)	7 (3.9)	.078
Known thoracic aortic aneurysm (surgically treated or not), n (%)†	0 (0)	13 (7.3)	.015
Known abdominal aortic aneurysm (surgically treated or not), n (%)	0 (0)	27 (15.1)	<.001
Familial history of aortic disease	2 (2.5)	13 (7.3)	.143
GFR, mL/min/1.73 m^2, median (IQR)	90 (75-106)	83 (64-101)	.379
Systolic blood pressure, mm Hg, median (IQR)	120 (120-130)	120 (120-140)	.064
Diastolic blood pressure, mm Hg, median (IQR)	80 (70-80)	70 (70-80)	.613
Maximum ascending aortic diameter, mm, median (IQR)	49 (45-51)	52 (48-56)‡	<.001

IQR, Interquartile range; *BMI*, body mass index; *SD*, standard deviation; *CAD*, coronary artery disease; *ACS*, acute coronary syndrome; *PTCA*, percutaneous transluminal coronary angioplasty; *CABG*, coronary artery bypass graft; *PAOD*, peripheral arterial occlusive disease; *TIA*, transient ischemic attack; *NA*, not applicable; *AAS*, acute aortic syndrome; *GFR*, glomerular filtration rate. *When the total cholesterol value was >200 or when the patient received lipid-lowering therapy. †Aneurysm in a thoracic aortic segment other than ascending. ‡Data available for 176 of 178 patients.

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TABLE E2. Histopathological findings in the study population (N = 255)

Parameter	Value, n (%)
Diagnostic group	
Inflammatory-atherosclerosis	9 (3.5)
Inflammatory-aortitis	8 (3.1)
Degenerative	172 (67.5)
Mixed: Degenerative-atherosclerosis	39 (15.2)
Mixed: Degenerative-aortitis	18 (7.1)
Mixed: Atherosclerosis-aortitis	3 (1.1)
Mixed: Degenerative-atherosclerosis-aortitis	6 (2.3)
Atherosclerosis grading	
Mild	81 (31.7)
Moderate	28 (10.9)
Severe	29 (11.3)
AHA lesion classification	
AHA 1	5 (1.9)
AHA 2	37 (14.5)
AHA 3	62 (24.3)
AHA 4	19 (7.4)
AHA 5	35 (13.7)
AHA 6	9 (3.5)
AHA 7	13 (5.1)
Atherosclerosis with excessive inflammation	1 (0.3)
Inflammatory atherosclerotic aneurysm	1 (0.3)
Aortitis, total	35 (13.7)
Aortitis patterns	
Granulomatous/giant cell	20 (7.8)
Lymphoplasmacytic	2 (0.7)
Mixed inflammatory	0 (0)
Suppurative	0 (0)
Unclassified	0 (0)
Healing/healed phase	13 (5.1)
Degenerative	235 (92.2)
Mucoid extracellular matrix accumulation	244 (95.6)
I-MEMA, total	201 (78.8)
I-MEMA grading	
Mild	72 (28.2)
Moderate	101 (39.6)
Severe	28 (10.9)
I-MEMA extent	
Focal	17 (6.6)
Multifocal	167 (65.4)
Diffuse	17 (6.6)
T-MEMA, total	234 (91.7)
T-MEMA grading	
Mild	87 (34.1)
Moderate	108 (42.3)
Severe	39 (15.2)
T-MEMA extent	
Focal	54 (21.1)
Multifocal	174 (68.2)
Diffuse	7 (2.7)

(Continued)

TABLE E2. Continued

Parameter	Value, n (%)
LMC, total	68 (26.6)
LMC grading	
Mild	16 (6.2)
Moderate	51 (20)
Severe	1 (0.3)
LMC extent	
Focal	40 (15.6)
Multifocal	26 (10.1)
Diffuse	2 (0.7)
EFTO, total	201 (78.8)
EFTO grading	
Mild	70 (27.4)
Moderate	101 (39.6)
Severe	30 (11.7)
EFTO extent	
Focal	21 (8.2)
Multifocal	163 (63.9)
Diffuse	17 (6.6)
EFFL, total	243 (95.2)
EFFL grading	
Mild	90 (35.2)
Moderate	97 (38)
Severe	56 (21.9)
EFFL extent	
Focal	51 (20)
Multifocal	179 (70.1)
Diffuse	13 (5.1)
ICI, total	219 (85.8)
ICI grading	
Mild	103 (40.3)
Moderate	100 (39.2)
Severe	16 (6.2)
ICI extent	
Focal	15 (5.8)
Multifocal	167 (65.4)
Diffuse	37 (14.5)
TCI, total	92 (36)
TCI grading	
Mild	6 (2.3)
Moderate	50 (19.6)
Severe	36 (14.1)
TCI extent	
Focal	32 (12.5)
Multifocal	58 (22.7)
Diffuse	2 (0.7)
Overall MD grading	66 (25.8)
Mild	
Moderate	130 (50.9)
Severe	38 (14.9)
Periaortitis, total	45 (17.6)

(Continued)

TABLE E2. Continued

Parameter	Value, n (%)
Periaortitis grading	
Mild	10 (3.9)
Moderate	26 (10.1)
Severe	9 (3.5)

AHA, American Heart Association; *I-MEMA*, intralamellar mucoid extracellular matrix accumulation; *T-MEMA*, translamellar mucoid extracellular matrix accumulation; *LMC*, laminar medial collapse; *EFTO*, elastic fiber thinning out; *EFFL*, elastic fiber fragmentation and loss; *ICI*, intralamellar collagen increase; *TCI*, translamellar collagen increase.

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TABLE E3. Histopathological findings according to age at presentation in patients with thoracic aortic aneurysm

Parameter	Patients age ≤65 y (N = 118; 46.3%), n (%)	Patients age >65 y (N = 137; 53.7%), n (%)	P value
Diagnostic group			
Inflammatory-atherosclerosis	3 (2.5)	6 (4.3)	.650
Inflammatory-aortitis	1 (0.8)	7 (5.1)	.112
Degenerative	99 (83.8)	73 (53.2)	<.001
Mixed: Degenerative-atherosclerosis	10 (8.4)	29 (21.1)	.008
Mixed: Degenerative-aortitis	5 (4.2)	13 (9.4)	.165
Mixed: Atherosclerosis-aortitis	0 (0)	3 (2.1)	.3
Mixed: Degenerative-atherosclerosis-aortitis	0 (0)	6 (4.3)	.059
Atherosclerosis grading			
Mild	41 (34.7)	40 (29.1)	.415
Moderate	8 (6.7)	20 (14.5)	.073
Severe	5 (4.2)	24 (17.5)	.001
AHA lesion classification			
AHA 1	3 (2.5)	2 (1.4)	.866
AHA 2	17 (14.4)	30 (21.8)	.168
AHA 3	32 (27.1)	30 (21.8)	.410
AHA 4	9 (7.6)	10 (7.2)	.920
AHA 5	9 (7.6)	26 (18.9)	.014
AHA 6	3 (2.5)	6 (4.3)	.651
AHA 7	1 (0.8)	12 (8.7)	.009
Atherosclerosis with excessive inflammation	0 (0)	1 (0.7)	.352
Inflammatory atherosclerotic aneurysm	0 (0)	1 (0.7)	.352
Aortitis, total	6 (5.1)	29 (21.1)	<.001
Aortitis patterns			
Granulomatous/giant cell	4 (3.3)	16 (11.6)	.026
Lymphoplasmacytic	0 (0)	2 (1.4)	.544
Mixed inflammatory	0 (0)	0 (0)	1
Suppurative	0 (0)	0 (0)	1
Unclassified	0 (0)	0 (0)	1
Healing/healed phase	2 (1.6)	11 (8)	.044
Degenerative	114 (96.6)	121 (88.3)	.026
Mucoid extracellular matrix accumulation	115 (97.4)	129 (94.1)	.325
I-MEMA, total	102 (86.4)	99 (72.2)	<.001
I-MEMA grading			
Mild	41 (34.7)	31 (22.6)	.045
Moderate	46 (38.9)	55 (40.1)	.951
Severe	15 (12.7)	13 (9.4)	.535
I-MEMA extent			
Focal	11 (9.3)	6 (4.3)	.184
Multifocal	83 (70.3)	84 (61.3)	.167
Diffuse	8 (6.7)	9 (6.5)	.946
T-MEMA, total	108 (91.5)	126 (91.9)	.897
T-MEMA grading			
Mild	43 (36.4)	44 (32.1)	.552
Moderate	49 (41.5)	59 (43)	.903
Severe	16 (13.5)	23 (16.7)	.589
T-MEMA extent			
Focal	26 (22)	28 (20.4)	.875
Multifocal	79 (66.9)	95 (69.3)	.783
Diffuse	3 (2.5)	3 (2.1)	.853

(Continued)

TABLE E3. Continued

Parameter	Patients age ≤65 y (N = 118; 46.3%), n (%)	Patients age >65 y (N = 137; 53.7%), n (%)	*P* value
LMC, total	31 (26.2)	37 (27)	.894
LMC grading			
Mild	10 (8.4)	6 (4.3)	.277
Moderate	20 (16.9)	31 (22.6)	.330
Severe	1 (0.8)	0 (0)	.940
LMC extent			
Focal	19 (16.1)	21 (15.3)	.865
Multifocal	10 (8.4)	16 (11.6)	.525
Diffuse	2 (1.6)	0 (0)	.413
EFTO, total	102 (86.4)	99 (72.2)	.009
EFTO grading			
Mild	42 (35.5)	28 (20.4)	.01
Moderate	45 (38.1)	56 (40.8)	.750
Severe	15 (12.7)	15 (10.9)	.809
EFTO extent			
Focal	12 (10.1)	9 (6.5)	.415
Multifocal	82 (69.4)	81 (59.1)	.112
Diffuse	8 (6.7)	9 (6.5)	.946
EFFL, total	109 (92.3)	134 (97.8)	.08
EFFL grading			
Mild	46 (38.9)	44 (32.1)	.311
Moderate	46 (38.9)	51 (37.2)	.873
Severe	17 (14.4)	39 (28.4)	.01
EFFL extent			
Focal	26 (22)	25 (18.2)	.550
Multifocal	79 (66.9)	100 (72.9)	.360
Diffuse	4 (3.3)	9 (6.5)	.386
ICI, total	107 (90.6)	112 (81.7)	.06
ICI grading			
Mild	59 (50)	44 (32.1)	.005
Moderate	43 (36.4)	57 (41.6)	.475
Severe	5 (4.2)	11 (8)	.324
ICI extent			
Focal	8 (6.7)	7 (5.1)	.765
Multifocal	80 (67.7)	87 (63.5)	.557
Diffuse	19 (16.1)	18 (13.1)	.623
TCI, total	28 (23.7)	64 (46.7)	<.001
TCI grading			
Mild	3 (2.5)	3 (2.1)	.853
Moderate	17 (14.4)	33 (24.1)	.07
Severe	8 (6.7)	28 (20.4)	.003
TCI extent			
Focal	12 (10.1)	20 (14.5)	.381
Multifocal	15 (12.7)	43 (31.3)	<.001
Diffuse	1 (0.8)	1 (0.7)	.915
Overall MD grading			
Mild	36 (30.5)	30 (21.8)	.155
Moderate	57 (48.3)	73 (53.2)	.504
Severe	21 (17.7)	17 (12.4)	.303

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TABLE E3. Continued

Parameter	Patients age ≤65 y (N = 118; 46.3%), n (%)	Patients age >65 y (N = 137; 53.7%), n (%)	*P* value
Periaortitis, total	10 (8.4)	35 (25.5)	<.001
Periaortitis grading			
Mild	2 (1.6)	8 (5.8)	.168
Moderate	6 (5.1)	20 (14.5)	.02
Severe	2 (1.6)	7 (5.1)	.257

AHA, American Heart Association; *I-MEMA*, intralamellar mucoid extracellular matrix accumulation; *T-MEMA*, translamellar mucoid extracellular matrix accumulation; *LMC*, laminar medial collapse; *EFTO*, elastic fiber thinning out; *EFFL*, elastic fiber fragmentation and loss; *ICI*, intralamellar collagen increase; *TCI*, translamellar collagen increase; *MD*, medial degeneration.

000   The complex interplay among atherosclerosis, inflammation, and degeneration in ascending thoracic aortic aneurysms

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Degenerative histopathology is the most frequent substrate in ascending thoracic aortic aneurysms, but atherosclerosis and inflammation contribute significantly to the development of chronic aortic thoracic disease.

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