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ORIGINAL ARTICLE

Clinicopathological study on penetrating atherosclerotic ulcers and aortic dissection: distinct pattern of development of initial event

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Abstract An intimal tear is responsible for the development of aortic dissection (AD). Plaque rupture is thought to progress to a penetrating atherosclerotic ulcer (PAU). However, the influences of mechanical stress and atherosclerosis on the intimal tear of AD and plaque rupture of PAU have not been fully understood. We enrolled 27 patients with AD [67.6 ± 11.2 years, female/male (F/M) 12/15] and 10 patients with PAU (71.0 ± 8.64 years, F/M 2/8) who underwent aortic reconstructive surgery in our hospital between 2007 and 2011. We analyzed the clinical data and morphological features of these patients and discuss the role of mechanical stress in the initial event. On clinical examination, hypertension was frequently observed in the patients of both the AD (77.8 %) and PAU groups (90.0 %), while hypercholesterolemia was significantly more prevalent in the PAU group (90.0 %) than in the AD (22.2 %) group. Most lesions of AD (96.3 %) were found in the ascending aorta up to the aortic arch, while those of PAU (90.0 %) were found in the descending and abdominal aortas. On pathological examination, the entrance tear was found in 21 (77.8 %) of the 27 patients with AD, and histologically comprised nonatherosclerotic intima and media. In contrast, the entrance tear was considered as plaque ulcer in 8 (80.0 %) of the 10 patients with PAU. The patients with PAU showed a significantly higher prevalence of soft plaque, complicated lesions, and medial fibrosis than those with AD, whereas patients with AD showed no complicated lesions and had a significantly higher prevalence of cystic medial necrosis than those with PAU. The present study suggests that less atherosclerosis and impairment of media could proceed to intimal tear formation in AD and that the disruption of the fibrous cap could cause the plaque ulcer of PAU.

Keywords Aortic dissection · Atherosclerosis · Clinicopathology · Mechanical stress · Penetrating atherosclerotic ulcer

Introduction

Acute aortic syndrome is recognized as a group of conditions with similar clinical profiles, including overt aortic dissection (AD), intramural hematoma, and penetrating atherosclerotic ulcer (PAU) [1]. Among these entities, AD and PAU are potentially lethal thoracic aortic pathologies. PAU was first described by Stanson et al. in 1986 [2] as an atheromatous ulceration that disrupts the internal elastic lamina and underlying media, with accompanying rupture, medial hemorrhage, or pseudoaneurysm formation. AD is defined as dissection of the aorta, characterized by the entry of blood into the aortic wall, usually between the outer third and inner two-thirds of the media. There are several differences in clinical presentation and pathological conditions between AD and PAU. Patients with PAU are somewhat older than those with AD and exhibit extensive atherosclerosis in the aorta and other arteries [3–5]. On the other hand, patients with AD tend to have mild atherosclerosis [5, 6].

AD and PAU progress with biochemical and biomechanical changes, and consequently rupture as mechanical events [7, 8]. AD has been believed to begin with the formation of a tear in the aortic intima that directly exposes

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the underlying diseased medial layer to the driving force of intraluminal blood [7]. PAU has been thought to originate from plaque ruptures on the aortic wall and to cause medial hemorrhage and pseudoaneurysm [2, 9]. However, few studies have been performed on the role of biomechanical factors in an initial event of AD and PAU.

The purpose of the present study was to compare the clinicopathological characteristics of AD and PAU, and to discuss the role of mechanical factors in the formation of entrance tears in patients with these lesions.

Materials and methods

Study population

By searching the surgical pathology files of the pathology department of Fukuoka University Hospital, we identified 165 patients who underwent aortic reconstructive surgery for AD or aortic aneurysm at Fukuoka University Hospital between January 2007 and December 2011. We retrospectively analyzed 37 consecutive patients (14 women and 23 men; age range 46–84 years; mean age 68.5 years) who were diagnosed with either aortic dissection (AD group) or penetrating aortic ulcer (PAU group). Diagnosis was confirmed by pathological examinations of surgical specimens and assessment of surgical records, including imaging of the aorta (Fig. 1). AD was defined as an aortic aneurysm with medial dissection that produced a false lumen filled with partly clotted blood (Fig. 2a–c). PAU was defined as an atheromatous lesion with ulceration that disrupted the internal elastic lamina and extended into the media, producing an intramural hematoma (Fig. 2d–f). Patients with known connective tissue disorders, including Marfan syndrome and Ehlers-Danlos syndrome, were excluded from the study. The study protocol was approved by the institutional review board of the Fukuoka University Hospital (No. 11-11-11). All procedures were performed in accordance with the guidelines of the institutional review board.

Pathological examination

The aortic tissues were excised as tubular segments or multiple pieces. All excised aortas were photographed and examined. Aortic wall specimens were fixed in 10 % neutral-buffered formalin and then processed for routine embedding in paraffin. Histological sections were prepared on all aortic samples. Sections were stained using hematoxylin-eosin, Masson-trichrome, and elastica Van Gieson stains. Because variations in histological changes were observed within a single case, the most severe changes were used for evaluation. Particular attention was paid to the changes in the intima and media, namely the presence of preoperative damage (intima: intimal tear, plaque ulcer, histological classification of atherosclerosis [10], and major plaque components [11]; media: false lumen, thrombosis, granulation tissue, fibrosis, and cystic medial necrosis). All histological sections were examined by a senior pathologist (N. S.) with an interest in cardiovascular disease.

Statistical analysis

Continuous variables were expressed as mean ± SD, and nominal variables were expressed as numbers and percentages. Continuous variables were compared using Welch's test. Fisher's exact probability test and the Chi-square test for an $m \times n$ contingency table were used for comparisons of categorical data. Data analyses were performed using StatFlex Version 6.0 (Artech Co. Ltd., Osaka, Japan). A P value <0.05 was considered statistically significant.

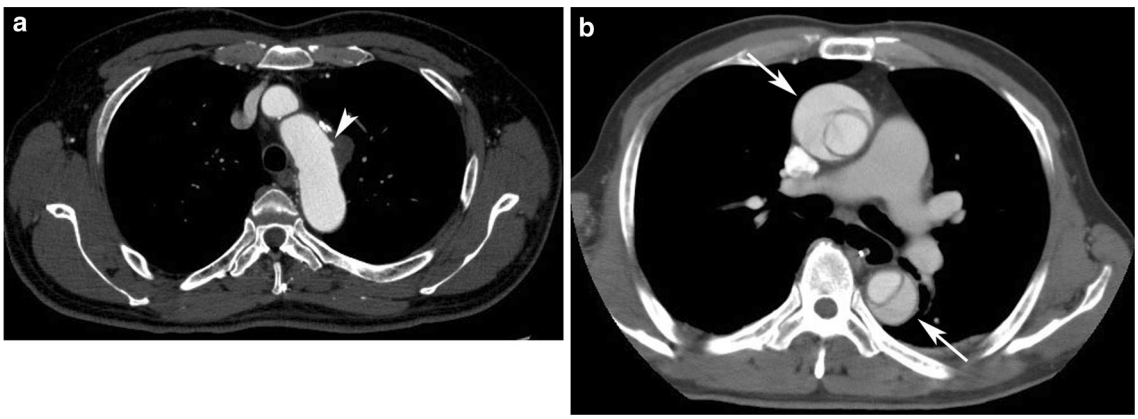

Fig. 1 CT scan of patients with penetrating atherosclerotic ulcer (**a**) and aortic dissection (**b**) at the level of aortic arch and ascending aorta, respectively. A contrast-filled penetrating atherosclerotic ulcer indicated by the *arrowhead* and the presence of false lumens of aortic dissection indicated by the *arrows*

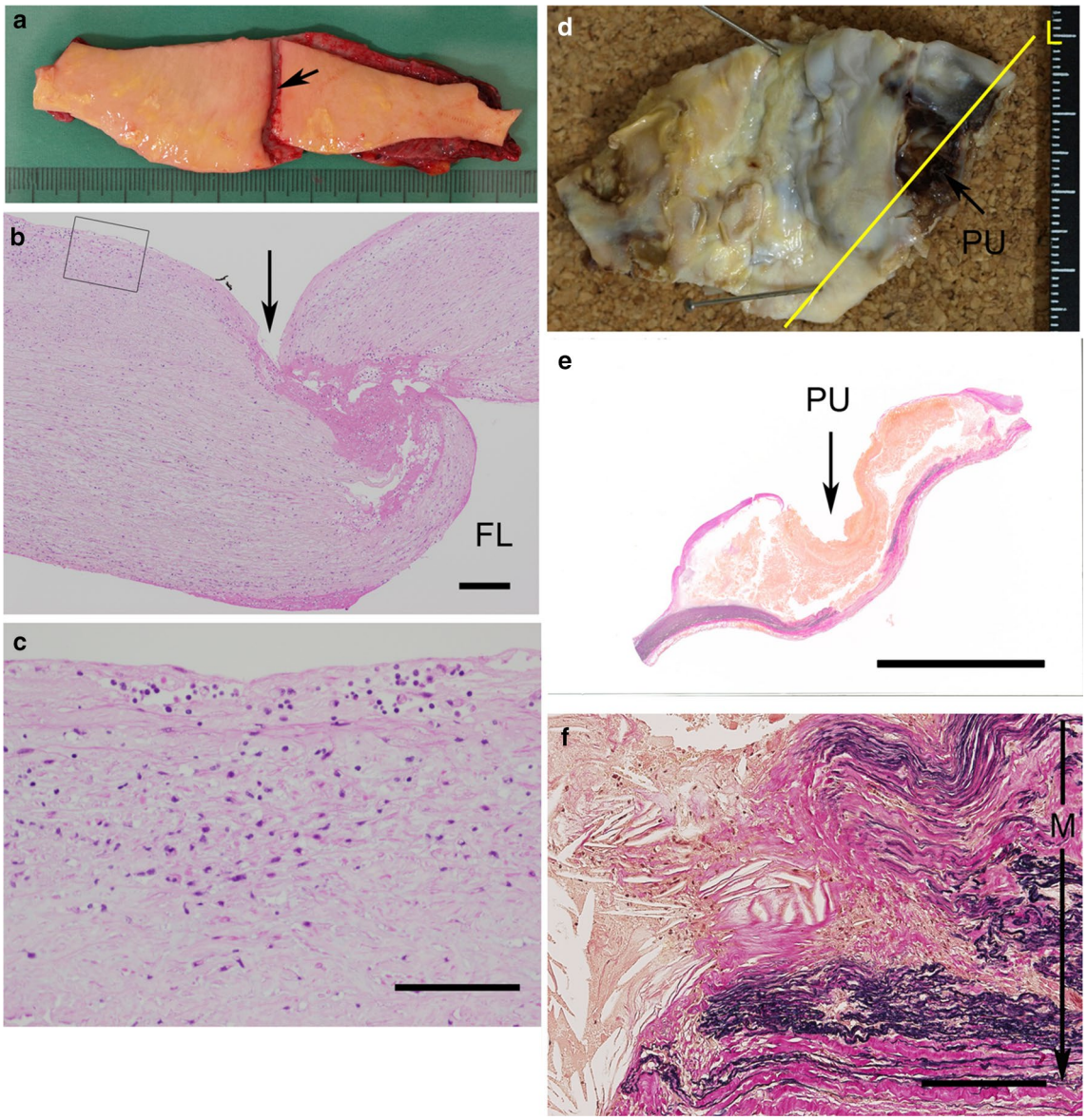

Fig. 2 A 79-year-old woman with aortic dissection (AD; **a**–**c**) and a 70-year-old man with penetrating atherosclerotic ulcer (PAU; **d**–**f**). **a** Macroscopic image of the aorta of the AD showing an intimal tear (*arrow*) without atheromatous plaque formation. The surrounding intima is smooth. **b** Low-power photomicrograph showing the splitting of the aortic wall within the media (false lumen *FL*), which communicates with the true lumen via the intimal tear (*arrow*). *Bar* 200 μm. **c** High-power photomicrograph showing the early lesion with luminal accumulation of foam cells and lymphocytes in the surrounding intima, which is indicated by the *box* in **b**. No atheroma formation can be seen. *Bar* 100 μm. **d** Photograph of the PAU specimen showing plaque ulceration (*PU*), which is associated with advanced atherosclerotic lesion. **e** The loupe view, indicated by *line L* in **d**, demonstrating a plaque ulcer (*PU*) with disruption of the fibrous cap and the false aneurysm with complete disruption of the media. *Bar* 10 mm. **f** High-power photomicrograph demonstrating hematoma containing atheromatous gruel, which penetrates into the adventitia, and complete disruption of elastin fibers of the media (*M*). *Bar* 200 μm. **b**, **c** Hematoxylin-eosin staining. **e**, **f** Elastica Van Gieson staining

Results

Comparison of clinical characteristics between the AD and PAU groups

The patients were classified into 2 groups based on pathological examination results of surgical specimens and surgical records as follows: those with AD ($n = 27$) and those with PAU ($n = 10$). Figure 1 shows the representative computed tomography (CT) images of patients with PAU and AD. CT in PAU clearly demonstrated a contrast-filled outpouching of the aorta in the absence of a false lumen (Fig. 1a). CT in AD showed the presence of both true and false lumens in the aorta (Fig. 1b). The clinical features of

the patients in the AD and PAU groups are summarized in Table 1. The mean age of the patients in the PAU group was 71.0 years, which was not significantly different from that of the patients in the AD group (mean age 67.6 years). Preoperative diagnoses were acute and chronic AD in 25 (92.6 %) and 2 patients (7.40 %) in the AD group, respectively. In contrast, the diagnoses were acute dissection and aortic aneurysm in 4 (40.0 %) and 6 patients (60.0 %) in the PAU group, respectively, which was significantly different from the diagnoses in the AD group ($P < 0.001$). Both the AD and PAU groups showed a high prevalence of hypertension (AD 77.8 %, PAU 90 %), but low incidence of diabetes mellitus (AD 3.70 %, PAU 20.0 %) and obesity (AD 25.9 %, PAU 10.0 %). In contrast, hypercholesterolemia was found in 9 (90.0 %) of the 10 patients in the PAU group, which was a significantly higher percentage than that in the AD group (22.2 %; $P < 0.001$). Most of the lesions of PAU (9/10, 90.0 %) were found in the descending and abdominal aortas, whereas 26 (96.3 %) of 27 AD lesions were found from the ascending aorta to the aortic arch.

Table 1 Clinical characteristics of the patients in the AD and PAU groups

	Groups		
	AD	PAU	*P*
No. of patients	27	10	
Mean age	67.6 ± 11.2	71.0 ± 8.64	0.339
Sex			0.173
Male	15 (55.6 %)	8 (80.0 %)	
Female	12 (44.4 %)	2 (20.0 %)	
Clinical diagnosis			<0.001
AD, acute type	25 (92.6 %)	4 (40.0 %)	
AD, chronic type	2 (7.40 %)	0 (0 %)	
Aortic aneurysm	0 (0 %)	6 (60.0 %)	
Risk factors of atherosclerosis			
Hypertension			0.373
Presence	21 (77.8 %)	9 (90.0 %)	
Absence	6 (22.2 %)	1 (10.0 %)	
Smoking			0.271
Presence	14 (51.9 %)	7 (70.0 %)	
Absence	13 (48.1 %)	3 (30.0 %)	
Hypercholesterolemia			<0.001
Presence	6 (22.2 %)	9 (90.0 %)	
Absence	21 (77.8 %)	1 (10.0 %)	
Diabetes mellitus			0.171
Presence	1 (3.7 %)	2 (20.0 %)	
Absence	26 (96.3 %)	8 (80.0 %)	
Obesity			0.287
Presence	7 (25.9 %)	1 (10.0 %)	
Absence	20 (74.1 %)	9 (90.0 %)	
Sites of lesions			<0.001
AsA and ArA	26 (96.3 %)	1 (10.0 %)	
DsA	1 (3.70 %)	2 (20.0 %)	
AbA	0 (0 %)	7 (70.0 %)	

Data are mean ± SD or *n* (%). Statistical analysis was performed using Welch's test, Fisher's exact probability test, and Chi-square test for $m \times n$ contingency table

AD aortic dissection, *PAU* penetrating atherosclerotic ulcer, *AsA* ascending aorta, *ArA* aortic arch, *DsA* descending thoracic aorta, *AbA* abdominal aorta

Comparison of pathological features between the AD and PAU groups

Histopathological features of the aorta were compared between the AD and PAU groups (Table 2). Entry into the dissection was observed in most cases of AD (77.8 %). On histological examination, the flap tissues were composed of atherosclerosis-free intima and media delaminated from the aortic wall (Fig. 2b, c). The entrance tear was considered as plaque ulcer in 8 (80.0 %) of the 10 patients in the PAU group, associated with a disrupted fibrous cap (Fig. 2d, e). All of the patients with PAU showed soft plaques and complicated lesions [type VI of the American Heart Association (AHA) classification]. In contrast, of the 27 patients with AD, none showed complicated lesions, but 12 (44.4 %) had preatheromatous lesions (types II and III of the AHA classification), and 15 (55.6 %) had atheromatous plaques (types IV and V of the AHA classification), which were composed of 10 (66.7 %) with soft plaques and 5 (33.3 %) with hard plaques. In the patients with AD, 14 (51.9 %) and 13 (48.1 %) of 27 false lumens were communicating and non-communicating types, respectively. In contrast, 8 (80 %) of 10 false lumens were the non-communicating type in patients with PAU. Thrombus was found in most of the false lumens in the patients with AD (85.2 %) and PAU (100 %). Fibrosis was significantly more prevalent in the wall of the false lumen in the PAU group (60 %) than in the AD group (11.1 %; $P = 0.008$). In contrast, cystic medial necrosis was significantly more prevalent in the AD group (55.6 %) than the PAU group (10.0 %; $P = 0.014$).

Discussion

PAU and AD are recognized as part of the spectrum of acute aortic syndrome because they have similar clinical manifestations and radiological features of rupture [1]. Acute aortic syndrome is characterized clinically by aortic-origin pain and coexisting hypertension. In the present study, hypertension was frequently observed in both the PAU (90 %) and AD groups (77.8 %). Twenty-five (92.6 %) of the 27 patients in the AD group and 4 (40 %) of the 10 patients in the PAU group were clinically diagnosed with

Table 2 Pathological features at the lesion sites in the AD and PAU groups

	Groups		
	AD	PAU	*P*
Intima			
Entrance tear			0.632
Presence	21 (77.8 %)	8 (80.0 %)	
Absence	6 (22.2 %)	2 (20.0 %)	
AHA classification of AT			<0.0001
Type II	10 (37.0 %)	0 (0 %)	
Type III	2 (7.41 %)	0 (0 %)	
Type IV	3 (11.1 %)	0 (0 %)	
Type V	12 (44.4 %)	0 (0 %)	
Type VI	0 (0 %)	10 (100 %)	
Atheromatous plaque			0.041
Soft	10 (66.7 %)	10 (100 %)	
Hard	5 (33.3 %)	0 (0 %)	
Media			
False lumen			0.084
Communicating type	14 (51.9 %)	2 (20.0 %)	
Non-communicating type	13 (48.1 %)	8 (80.0 %)	
Thrombosis			0.265
Presence	23 (85.2 %)	10 (100 %)	
Absence	4 (14.8 %)	0 (0 %)	
Granulation tissue			0.116
Presence	4 (14.8 %)	4 (40.0 %)	
Absence	23 (85.2 %)	6 (60.0 %)	
Fibrosis			0.008
Presence	3 (11.1 %)	6 (60.0 %)	
Absence	24 (88.9 %)	4 (40.0 %)	
Cystic medial necrosis			0.014
Presence	15 (55.6 %)	1 (10.0 %)	
Absence	12 (44.4 %)	9 (90.0 %)	

Data are presented as *n* (%). Statistical analysis was performed using Fisher's exact probability test and Chi-square test for $m \times n$ contingency table

AD aortic dissection, *PAU* penetrating atherosclerotic aortic ulcer, *AT* atherosclerosis

acute AD. These findings are consistent with the clinical characteristics of acute aortic syndrome.

The role of atherosclerosis in the progression of AD is controversial. Some investigators do not consider atherosclerosis as a risk factor of AD [5, 7, 12]. On the other hand, a few reports suggest that rupture of ulcerocalcific aortic atheromas may have initiated the intimal tear in AD, particularly in type III dissection [13]. In the present study, the flap of AD was composed of nonatherosclerotic intima and media. The patients with AD showed no complicated lesions of atherosclerosis. On clinical examination, the patients with AD showed a high prevalence of hypertension, but low prevalence of hypercholesterolemia, diabetes mellitus, and obesity. These findings suggest that atherosclerosis may not be a risk factor for AD, which is consistent with previous reports [5, 7, 12].

In the present study, hypertension was found in most of the patients with AD and PAU. In contrast, severe atherosclerosis was not associated with AD, but with PAU, also consistent with previous reports [5, 7]. Hypertension has always been considered the mechanical force that finally leads to aortic wall rupture [14]. In our previous study [15], patients with AD, but without Marfan syndrome showed significantly greater distensibility and decreased elastin content of the aortic wall than age-matched control subjects. Therefore, the aorta of AD patients is dilated and the wall stress increases even more under normal blood pressure. In the setting of hypertension, wall stress can exceed the holding power of the internal layer of the aorta, causing an intimal tear. In contrast, the present study showed that atheromatous plaques were soft and complicated in all patients with PAU. Thus, the entrance tear was considered a plaque ulcer in most patients with PAU. Plaque ulcer can result from the disruption of the fibrous cap. In a previous study [16], a uniaxial stretching test revealed that the fibrous cap was stiffer than the media and nonatherosclerotic intima. Thinning of the fibrous cap is a critical feature of vulnerable atheromatous plaque. The thin fibrous cap can cause a significant increase in stress and can be overwhelmed by the increment in mural stress caused by hypertension, resulting in plaque rupture. Thus, there is the possibility that hypertension triggers the initial wall rupture of AD and PAU by different mechanisms.

The development of atherosclerosis depends on various risk factors, including aging, diabetes mellitus, hypertension, and hypercholesterolemia [17]. Hypertension and hypercholesterolemia are major risk factors and have different effects on the progression of atherosclerosis [18–20]. Hypertension is related to an increase of intimal collagen and/or proteoglycan content in arteries, causing increased intimal thickness and stiffness. In contrast, hypercholesterolemia is associated with the increase of extracellular lipid deposition and foam cell population in arterial intima, resulting in atheroma formation [21]. It has been shown that a vulnerable atheromatous plaque with thin fibrous cap and large atheromatous core relates to plaque rupture [22]. In this study, the incidence of hypercholesterolemia was significantly higher in patients with PAU than in those with AD. Pathologically, all patients with PAU had soft and complicated plaques in the aorta. These findings suggest that vulnerable plaque may be the critical lesion predisposing to PAU.

In this study, severe atherosclerosis was the underlying lesion of PAU, but not of AD. Atherosclerotic plaques are not distributed equally in the vascular tree

[23, 24]. Flow-related biomechanical factors, particularly wall shear stress, are thought to be associated with the regional development of atherosclerotic plaques, which are more prevalent in the inner curve of coronary and carotid arteries exposed to low wall shear stress [24, 25]. Similarly, complex plaques have been shown to develop predominantly at the inner curvature of the aortic arch and of the descending aorta, which are exposed to low wall shear stress and high oscillatory shear stress [26]. In this study, PAU was more prevalent in the descending and abdominal aorta than the ascending aorta. This finding may be related to the predilection sites of atherosclerotic plaques, induced by flow-related biomechanical factors.

Although plaque ulcer commonly develops in advanced atherosclerosis, it is usually defined in the intimal layer and not associated with intramural hematoma [27]. When the atheroma penetrates the media, the media is exposed to pulsatile arterial flow that generates hemorrhage in the media, resulting in PAU (Fig. 2e, f) [28]. Atherosclerotic plaques are reported to express high levels of tissue factor that induce thrombosis after plaque rupture [29]. In this study, all of the patients with PAU had complicated lesions and medial thrombosis. In addition, the prevalence of medial fibrosis was significantly higher in patients with PAU than in those with AD. These findings are consistent with the results of a previous study [2].

Some limitations should be considered in interpreting our results. First, because of the small number of subjects in this study, some variables were not suitable for statistical analysis. Our focus addressed mainly the effects of hypertension and atherosclerosis on the development of AD and PAU, particularly on the formation of entrance tears in these lesions. Our results regarding hypertension, hypercholesterolemia, and atherosclerosis were consistent with those of previous studies. However, these data need to be confirmed in larger studies. Second, a shortcoming of this study was that the surgical aortic samples contained lesions of AD and PAU, including an entrance tear, but not whole aortic tissues. Atherosclerosis is a systemic lesion, including the number, size, depth, and quality of plaques. Pathological examination of these variables in the whole aorta was difficult in this study. Finally, the prevalence of cystic medial necrosis was somewhat higher in this study than in previous studies [30, 31]. Although the reason for this difference is unclear, previous studies [15, 30] reported decreased elastin fibers in the media of AD. In addition, our previous study [15] demonstrated the negative correlation between distensibility and elastin contents in the media of AD. Therefore, medial impairment, including cystic medial necrosis and decreased elastin contents, could progress to intimal tear formation in AD.

Conclusions

The present study showed that (1) hypertension was a critical risk factor for PAU and AD; (2) severe atherosclerosis, including vulnerable plaques and complicated lesions, was relevant to PAU, but not to AD; and (3) cystic medial necrosis was more prevalent in AD than in PAU.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

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