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Cystic medial necrosis: pathological findings and clinical implications

Necrose cística da média: manifestações patológicas com implicações clínicas

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Resumo

A necrose cística da média (NCM) é uma desordem das grandes artérias, em particular a aorta, caracterizada por acúmulo de substância basofílica na camada média com lesões císticas-símile. É sabido que a NCM ocorre em certas doenças do tecido conjuntivo tal como síndrome de Marfan, síndrome de Ehlers-Danlos, e ectasia ânulo-aórtica, que normalmente resulta de mudanças degenerativas na parede aórtica. A relação entre NCM e defeitos congênitos do coração, assim como outras desordens, tem sido evidenciada. Os mecanismos são ainda controversos, embora muitos estudos moleculares tenham sido conduzidos. O objetivo do presente artigo é fornecer uma visão geral da NCM em termos de características patológicas, implicações clínicas e etiologia baseada em resultados de pesquisa molecular.

Descritores: **Aorta. Anormalidades Cardiovasculares. Tecido Conjuntivo, Patologia Clínica.**

Abstract

Cystic medial necrosis (CMN) is a disorder of large arteries, in particular the aorta, characterized by an accumulation of basophilic ground substance in the media with cyst-like lesions. CMN is known to occur in certain connective tissue diseases such as Marfan syndrome, Ehlers-Danlos syndrome, and annuloaortic ectasia, which usually result from degenerative changes in the aortic wall. The relationships between CMN and congenital heart defects as well as other disorders have been evidenced. The mechanisms are still controversial, even though many molecular studies have been conducted. The aim of the present article is to provide a comprehensive overview of the CMN lesion in terms of pathologic features, clinical implications and etiologies based on molecular research results.

Descriptors: **Aorta. Cardiovascular Abnormalities. Connective Tissue. Pathology, Clinical.**

NORMAL AORTA

The normal thoracic aorta is composed of an aortic media with regular elastic lamellae alternating with smooth muscle cell layers aligned between the normal elastic lamellae [1]. Layers of endothelial cells constitute aortic intima lying on the internal elastic lamina [2]. In the normal aorta, well-formed elastin fibers display in a lamellar pattern (Figure 1).

CYSTIC MEDIAL NECROSIS (CMN) (DISEASED AORTA) CONCEPT

CMN is a disorder of large arteries, in particular the aorta, characterized by an accumulation of basophilic ground substance in the media with cyst-like lesions. In the media, degenerative disruptions of collagen, elastin and smooth muscles may result in weakening of the arterial wall

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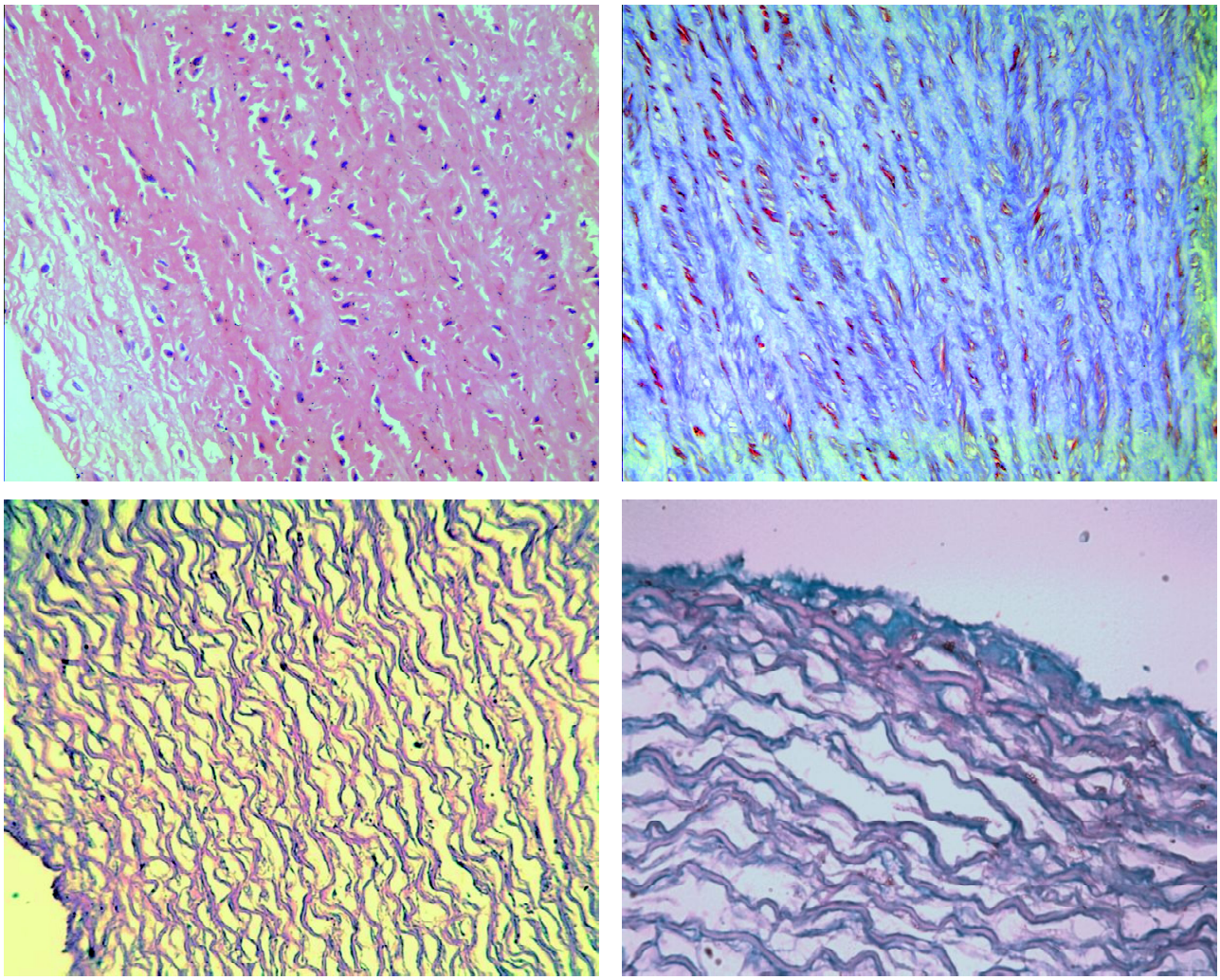

Fig. 1 – Histological appearance of the aortic media and intima within the normal structures of a healthy subject. (A) The aortic wall structures were intact, the intima was intact and the smooth muscle cells were abundant. H&E×400; (B) The normal aorta had very few collagens. Masson×200; (C) The normal aorta had intact and regular arrayed elasitic fibers in the intima and media. van Gieson×400; and (D) Very few acid mucopolysaccharides were deposited in the normal aorta. AB-PAS×400

[3]. CMN in aortic dissection was initially described by Babes and Mironescu, in 1910, but attracted little interest [4]. Until after 1928, it were Gsell and Erdheimin who proposed the concept of idiopathic CMN attracting considerable attention, which was recognized related to aortic aneurysm, dissection, and rupture and Marfan's syndrome [5]. CMN is not the cause but is a common pathological finding, probably as a result of primary disorder, like fibrillin defficiency in some, or advanced apoptosis in others. CMN is a common finding in the elastic arterial specimens and the difference between normal and abnormal is the amount of ground substance in the media layer. Also the presence of abnormal amount of elastic fragmentation and mucle cell apoptosis or disruption is common in these "abnormal" specimens, as described by Carlson et al. [6]. This concept is important to understand why the prevalence changes a lot among different papers. The pathogenesis of these aortopathies has now been considered more a consequence of the aortic wall weakness. In particular, in Marfan´s syndrome, fibrillin-1 deficiency can be more related to aortic wall medial fragility, which is histologically traduced by CMN, elastic fragmentation and smooth muscle cell apoptosis or necrosis [1]. The term "CMN" is sometimes replaced by "cystic medial degeneration", as necrosis is not always present in the pathological process and the latter can be the underlying attributable factor responsible for a rupture of the vasa vasorum [3].

Erdheims terms have no doubt been popularly accepted as to describe the underlying pathology of aortic medial degeneration leading to aortic disorders. However, some authors denied this statement as they claimed that only a minority of patients with aortic dissection had medial degeneration [7,8]. In 1977, Schlatmann and Becker [9] proposed that the word "cystic" in the term was inappropriate, since the lesions did not form true cysts, but medial structural defects with the semifluid ground substance instead. The term "medial necrosis" was not justified either, because necrosis was seldom encountered in the lesions of the media. Similarly, Hirst and Gore [10] observed that CMN was actually the degeneration, swelling and disruption of elastic fibers and smooth muscle cells with scattered mucoid accumulation, thereby enlarging the tissue gaps, but no cysts were found. Roberts [11] studied the changes in aortic aneurysms without finding any fundamental differences between aneurysmal and normal aortas. Nakashima et al. [12] noticed apparently irregular arrangement and shape, and decreased in number in the interlaminar fibers of the aorta, resulting in a rarefaction of interconnection between the elastic laminae in the media. In spite of diverse opinions based on the above observations, however, the concept of CMN is still the overwhelming term used today.

PREVALENCE

In fact, the prevalence of CMN varies on the basis of the underlying diseases. It was estimated to be 6% in the patients with thoracic aortic aneurysm [13]. By histology, it was identified in 42.9% (3/7) patients with Turner's syndrome [14]. This lesion may also involve the carotid arteries [15]. In 100 consecutive aortic aneurysmal patients, their ascending aortic aneurysm were atherosclerotic in 69%, CMN in 22%, and leutic in 9% [16]. In patients receiving surgical treatment for aortic dilation with aortic valve disease, the incidence of CMN was 100% as described by Agozzino et al. [17]. In the ascending aortic wall of patients with tetralogy of Fallot, pathological study revealed fibrosis in 82%, elastic fragmentation in 59%, CMN in 35% and medionecrosis in 29% [18]. In a clinicopathological study including 513 consecutive ascending aortic surgical specimens, CMN was present in 40.7% of the patients, and in 56 (51.4%) of 109 patients with aortic dissection [19].

HISTOLOGY

In 1942, Davies described CMN in a 36-year-old patient with aortic valve insufficiency, aortic dilation and heart failure. Histology revealed areas of degeneration with cystic changes, loss of elastic and muscle fibres in the aortic media, with accumulation of mucopolysaccharide and cyst-like pools between the fibres [20]. Collagen cross-linking defect and elastic tissue depletion in the media constitute the pathological basis of the development of CMN [21]. In "healed aortic dissection", the media and intima was replaced by fibrous tissue in addition to multiple foci of CMN [22]. The amount and organization of the elastin in the aortic aneurysm segments from patients with Marfan syndrome compared with normal aorta [23]. In 1970, Carlson et al. [6] defined grading of CMN into 4: Grade 1, no distinct cyst formation with intact elastic tissue; Grade 2, small distinct cyst with intact elastic tissue; Grade 3, moderate number of cysts with focal disrupted elastic tissue; and Grade 4, widespread large cysts with interrupted and retracted elastic tissue.

In 1981, Loeppky et al. [24] made detailed descriptions of pathological observations of CMN. They found, against the remaining media, there were fragmentation and focal loss of elastica and smooth muscles; while within the remaining media, there were focal fibrosis and band-like necrosis. Small cysts with focal vascularization could be visualized within the inner media. The adventitia was densely fibrotic and contained occasional lymphoid aggregates. Later, Klima et al. [25] noted that both elastic fragmentation and cystic medial change were present in a high percentage of patients, and that CMN was inversely correlated with increasing age of patients. In 1987, Isner et al. [26] initiated a semiquantative shema of CMN according to the demoain of the arterial involvement: 0: absent CMN; 1+: subintimal; 2+: subadventitial; and 3+: full-thickness.

CMN is usually present in young patients. The medial age of the patients with Marfan's syndrome in the presence of CMN was 32 years, while those patients without Marfan were at the age of 50 years [27]. CMN of the aorta was even found in neonate [28], and in childhood [29]. CMN of the aortic tissue of the patients with bicuspid aortic vavle under van Gieson staining may illustrate fragmentations of elastic fibres and accumulation of extracellular matrix [30]. Ultrastructure of CMN may show disorganized, haphazard architecture of the media [31], or cribrose media with effuse intima at lower magnification, and normal or fragmented elastic fibers with large cavities at higher magnification [32].

CLINICAL IMPLICATIONS

As one of the pathological changes of the aorta, CMN was often observed in cardiac surgical patients. This lesion often involves thoracic and abdominal aorta, and was often present in the patients with benign hyperplasia of the vascular wall and cocaine abuse, in addition to aortic dissection, aortic aneurysm [15,33], and Turner's syndrome [15]. CMN of the aorta in the patients with Turner's syndrome can be the cause of aortic dissection [34] and death [35]. CMN is known to occur in certain connective

tissue diseases such as Marfan's syndrome [36], Ehlers-Danlos syndrome [37], and annuloaortic ectasia [38], which usually result from aortic wall fragility due to degenerative changes. In patients without Marfan's syndrome, CMN occurs more frequently in geriatric and hypertensive individuals [39]. Ueda et al. [27] reported 46 patients with or without Marfan's syndrome, all of whom had histological evidence of CMN. Both groups had similar aortic dissection rates, but annulo-aortic ectasia was more frequently in those with Marfan's syndrome than those without (81% vs. 46%, $P < 0.05$). The aortic dilation caused by CMN was usually limited in the ascending aorta, and rarely involved the aortic valve ring and sinuses of Valsalva [5].

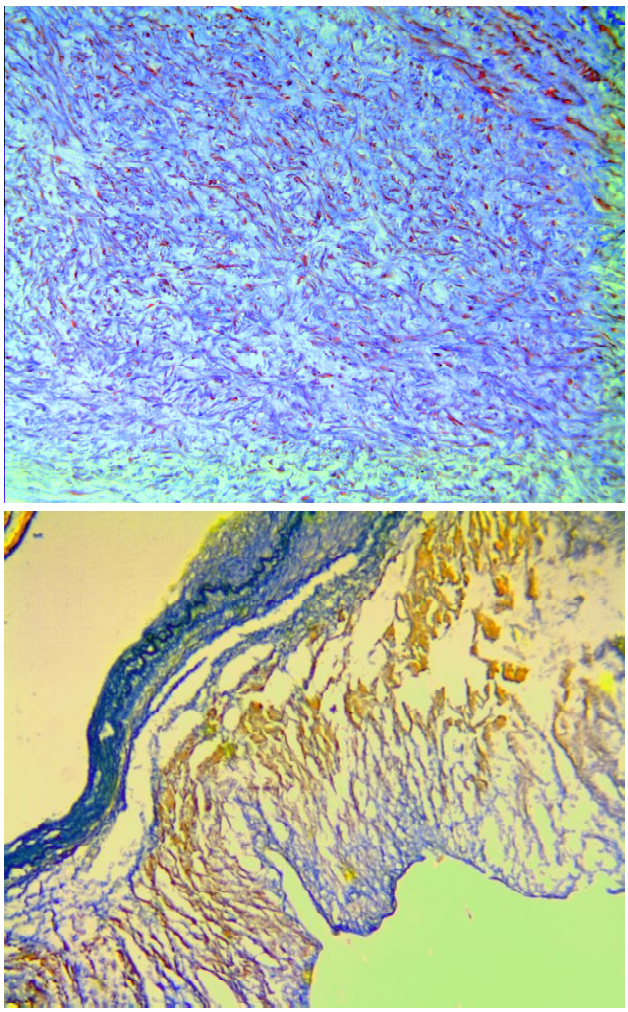

Fig. 2 – Marfan's aortic tissues showing cystic medial necrosis with (A) smooth muscle cell fragmentation and more collagen deposition, Masson×200; and (B) proliferation and disruption of the intima (blue), and smooth muscle cell fragmentation (yellow) and collagen deposition (red) in the media. VG-Victoria blue bichrome staining×100

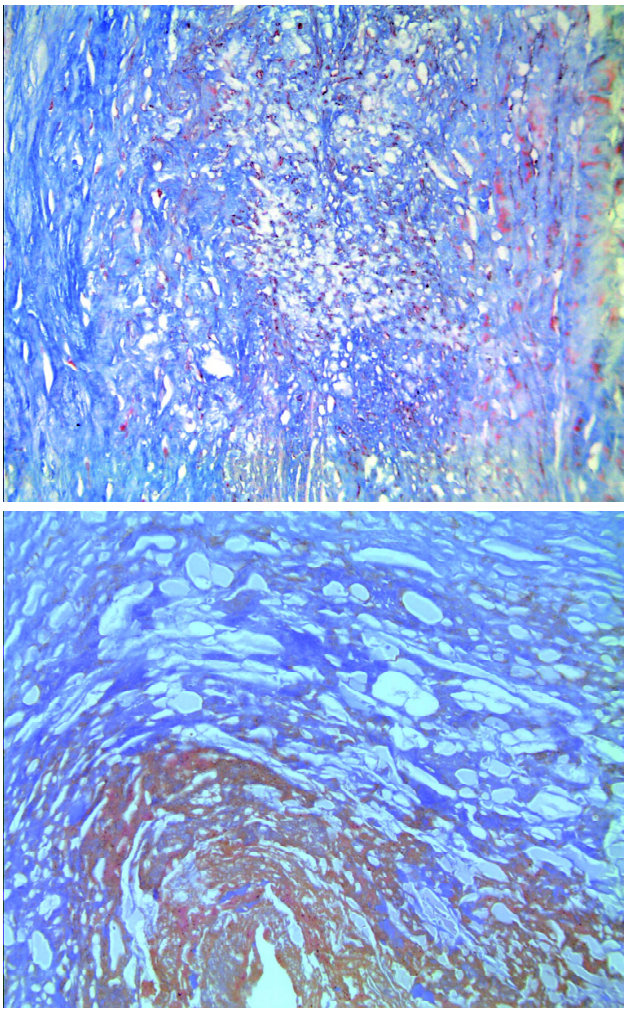

Fig. 3 – Cystic medial necrosis of ascending aortic aneurysm of (A) a 47-year-old male patient diagnosed of ascending aiortic aneurysm, showing much collagen deposition in the intima and smooth muscle cell fragmentation with few collagen and cystic-like lesions in the media, and (B) another 47-year-old male patient diagnosed of ascending aortic aneurysm with aortic insufficiency and stenosis, showing degenerative disruptions elastic fibers and smooth muscle cells with few collagen but more cystic-like lesions in the media. Masson×200

CMN was once observed in the patients with aortic stenosis [33]. Associations between CMN and congenital disorders were also observed. The evidences of coarctation of the aorta and bicuspid aortic valve associated with CMN were described by several authors [26,40,41]. Patients with bicuspid aortic valve and aortic aneurysm presented CMN not related to the age [42]. Although CMN may be seen in dilated aortas associated with Marfan's syndrome and bicuspid aortic valve, but it is still controversial in whether CMN may directly result in aortic dissection [43]. Long-term exposition to growth hormone excess may predispose

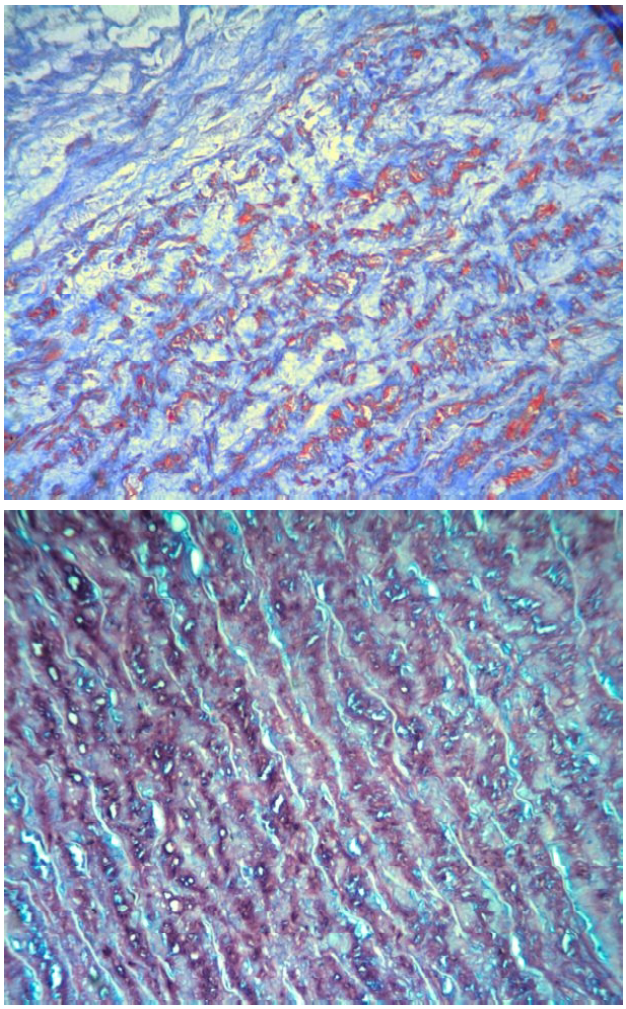

Fig. 4 – Histology of the ascending aorta of a 44-year-old female patient with acute type A aortic dissection, showing (A) retained aortic wall structures with more collagens and cystic-like lesions. Masson×200; and (B) Small focal cystic-like lesions with acid mucopolysaccharides accumulation in the retained aortic media indicating a Grade 2-3 cystic medial necrosis. AB-PAS×200

the development of CMN by heralding connective tissue defects [44], as in the patient with acromegaly [45], or with systemic lupus erythematosus [46], or in drug addict [47]. Growth hormone excess can be associated with excess mucopolysaccharide deposition characteristic by both CMN and extensive myxomatous degeneration, which even invading all four cardiac valves [44]. CMN can be the underlying cause of heterogeneous Marfan's syndrome [48,49], aneurysm of the circumflex coronary artery [50], spontaneous dissection of the internal thoracic artery [49], aortic valve commissure tear [51], spontaneous dissection of massive bilateral sinus of Valsalva aneurysms [52], pulmonary artery aneurysm [53], and carotid artery aneurysm [20]. Aortic root aneurysm due to donor CMN after heart-lung transplantation was also noted [54].

Normal individuals, with no aortic disease may also have CMN in the aorta, even children with normal aorta may have small amount of ground substances in the elastic arteries, aorta and pulmonary artery, but the grade of CMN can vary in amount (personal communication). Besides, Marfan's syndrome (Figure 2), aortic aneurysm (Figure 3), and aortic dissection related CMN (Figure 4), we noted CMN in the ascending aorta of the patients with coronary artery disease (Figure 5), and even in the aorta of normal subjects (Figure 6).

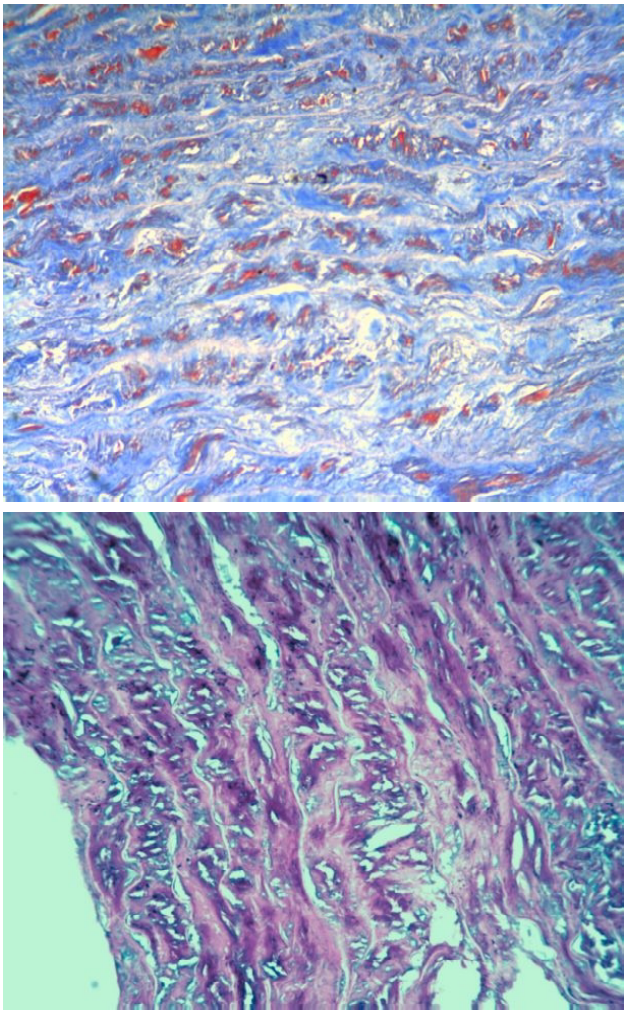

Fig. 5 – Histology of the ascending aorta of a 59-year-old male patient with coronary artery disease. The specimen was taken from the proximal anastomotic sites of the ascending aorta during coronary artery bypass grafting. (A) More collagens deposited in the disrupted aortic media; Masson×200; (B) More extensive and small and moderate cystic-like lesions in the aortic media. AB-PAS×200

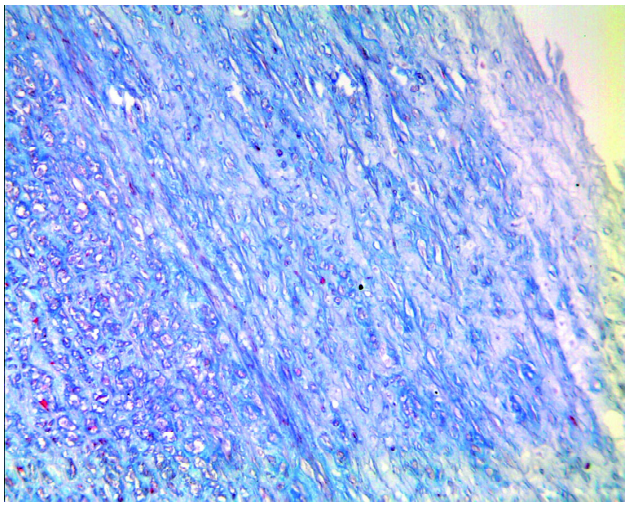

Fig. 6 – Histology of the ascending aorta of a 45-year-old male healthy subject showing more collagen deposition and extensive cystic-like lesions in the aortic intima and media. Masson×200

Due to the susceptibility to dissection and rupture, patients with CMN of the aorta of any etiology should be managed properly [55]. Treatment of the aortopathies relating to CMN of the aorta is difficult and entails both antihypertensive and surgical therapy. Surgical procedures vary depending on the natures, the severities, and the extensiveness of the CMN lesions in the aorta or other large vessels. Marsalese et al. [39] reported 97% of the patients diagnostic of CMN in patients without Marfan's syndrome received Bentall operation had an overall estimated 1-, 3- and 5-year survivals of 72.2%, 63.5% and 57.4%, respectively. In Marfan and non-Marfan patients with histologically evidenced CMN, cardiovascular event-free rate at 10 years was for 28% Marfan patients and 68% for non-Marfan patients [27]. Reimplantation procedures with a tube graft, a tube graft with creation of neo-sinuses, and a Valsalva graft obtained a 100% survival at the follow-up of 3.7 ± 3.4 years [56].

MOLECULAR FINDINGS

De Sá et al. [57] noted a reduced fibrillin-1 content in both ascending aorta and pulmonary trunk in patients with a bicuspid aortic valve. CMN and elastic fragmentation, similar to Marfan's syndrome, were noted in histological specimens. They explained that abnormalities in different phases of cell migration of the neural crest may be responsible for the development of the bicuspid aortic valve. Fibrillin-1 deficiency in the aortic tissues of patients with bicuspid aortic valves might trigger matrix metalloproteinase production, leading to matrix disruption and dilation [58]. The research findings were in agreement with the those on embryos of Syrian hamsters reported by Sans-Coma et al. [59], who proposed that aortic wall fragility was closely related to the formation of bicuspid aortic valves. By comparison, bicuspid aortic valve type A (fusion of left coronary and right coronary cusps) may have more severe degeneration in the ascending aorta than the type B (fusion of right coronary and noncoronary cusps) [60]. Furthermore, aortopathies like coarctation, aneurysm formation, and dissection may have intrinsic correlations with the bicuspid aortic valve, and might be the underlying causes of aortic wall fragility [61]. Recently, autosomal dominant inheritance of bicuspid aortic valve and aortic dilation was investigationally proved in several families with a positive history of aortic dissection [62].

Research of inducible vascular smooth muscle-specific apoptosis in a mouse model revealed vascular smooth muscle cell apoptosis may lead to induced medial expansion, increased elastic lamina breakdown, and abnormal matrix deposition [63]. Experimental studies showed that CMN of the aorta was characterized by p53 accumulation, Bax upregulation, cell death by apoptosis, and cell regeneration [64]. In the RECS1 (a shear stress-responsive gene and a negative regulator of matrix metalloproteinase-9 production) knockout mice, dilated aorta with CMN was of increased aortic gelatinase activities [65].

In the aortic wall of Marfan patients, type 1 angiotensin II receptor (AT1R) expression was significantly decreased, and type 2 angiotensin II receptor (AT2R) expression was significantly increased in comparison to the control. Further investigations illustrated that both the angiotensin-converting enzyme inhibitors and type 2 angiotensin II receptor (AT2R) blocker significantly inhibited vascular smooth muscle cell apoptosis [66]. In CMN areas, immunoreactivity against peroxisome proliferator-activated receptor-γ was observed in the nuclei of vascular smooth muscle cells. Inflammatory cells, either macrophages or T lymphocytes were absent in CMN [67]. Segura et al. [68] found CMN with loss of elastic fibers and smooth muscle cells in thoracic aortic aneurysm. Areas of CMN did not show any immunoreactivity for any matrix metalloproteinases or tissue inhibitors of metalloproteinases.

Comparing with Marfan or normal control, Loeys-Dietz syndrome samples had less medial degeneration, but more diffuse CMN, collagen deposition, severe elastic fiber fragmentation and glycosaminoglycan deposition as shown on hematoxylin and eosin and Movat pentachrome stainings. Increased transforming growth factor-β signaling and phosphorylated Smad2 expressions were evidenced by immunohistochemical staining [69]. Transforming growth factor-β and CD56 were both detcted in the atherosclerosis area and in the CMN lesion without atheromatous deposit in the aortic aneurysms, respectively. There were more

transforming growth factor-β-positive cells in the atherosclerostic region, while rarely were the cells seen in the CMN [46].

SUMMARY

CMN may develop in the aortic tissues of patients with various aortopathies, such as Marfan's syndrome, aortic aneurysm, aortic dissection, atherosclerotic disease, congenital heart disease and even healthy individuals. Aortic wall fragility can be the main cause responsible for the occurrance of CMN. Molecular findings including apoptosis and transforming growth factor-β expression alterations may at least explain in part the rationale of CMN. Both antihypertensive and surgical treatments as well as close follow-up are recommended for patients with CMN. In short, CMN is related with aortic fragility but we still believe that it is a part of a more complex degenerative process, probably a consequence of molecular process and mechanical stress that impacts on the aorta or other elastic vessels. It may also be associated with elastic fragmantation and mucle cell degeneration.

In conclusion, CMN is a pathological phenomenon frequently observed in the aorta of the patients with aortic disorders. It may predispose fragility of the aortic wall media, a risk factor responsible for the development of these aortopathies. Further comprehensive studies that may help understanding the underlying etiologies are necessary.

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