EDITORIAL

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Sorting out aortic aneurysms: A team enterprise

Aortic aneurysms present considerable diagnostic and treatment challenges. These difficulties relate to diverse etiologies, incomplete understanding of pathogenesis, and variations in presentation and disease course. The clinician may see this either as frustrating conundrums or fascinating opportunities for which pathways exist to provide satisfying outcomes in most cases.

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NOT JUST A CONDUIT: THE PROXIMAL VS DISTAL AORTA

The differences between thoracic aortic aneurysms (TAAs) and abdominal aortic aneurysms are instructive apropos embryogenesis, vessel function, and disease vulnerability. For example, most muscular blood vessels contain smooth muscle cells derived from embryonic mesoderm. However, the proximal aorta and its proximal arch branch vessels have muscle cells derived from neuroectoderm. Modifications in embryogenesis continue caudally and within branch vessels, leading to specialization of the vascular tree to suit the organs that each aortic segment and branch vessel supplies.[1,2] Aortic wall thickness, density of vasa vasora, and elastic fiber content all diminish from proximal to more distal aortic segments.[3]

Gene expression studies have demonstrated that at least 17% of the aortic wall genome differs between the thoracic aorta and abdominal aorta.[4] In vitro studies have revealed different responses of proximal and distal aortic wall smooth muscle cells to the same stimuli (eg, transforming growth factor beta), reflecting lineage and territory-specific specialization, function, and vulnerabilities.[1] Muscular vessels are also immunologically competent organs, being equipped with dendritic cells with Toll-like receptors that are pathogen-sensing and present pathogen-associated molecules to T cells. These too differ with vessel territories.[5]

In terms of organ targeting, atherosclerosis is more common and severe as the aorta traverses the chest and abdomen, with 95% of atheromatous aneurysms located below the renal arteries.[6] Conversely, inflammatory aortic aneurysms are most common in the thoracic aorta, especially within its proximal distribution. It has long been appreciated that unique inherent properties of thoracic vs abdominal aortic walls are more critical than their location in establishing disease vulnerabilities.[7] Thus, the concept of the aorta and other vascular channels being merely conduits for blood flow is incomplete and ignores differentiation that occurred during embryogenesis and adaptation to pressure, turbulence, and organ and tissue requirements. And this story becomes still more interesting as vascular territories change their biochemical, physical, and functional properties with aging and comorbidities acquired through life's journey.[6,8]

INFLAMMATORY VS NONINFLAMMATORY ANEURYSMS

Distinctions in aorta topography become more interesting in disease context. Noninflammatory TAAs have been associated with hypertension, smoking, bicuspid aortic valves, Turner syndrome (45 monosomy X or incomplete X karyotype), and a variety of genetic anomalies affecting vessel matrix (eg, fibrillin and collagen). Many matrix disorders (eg, vascular ectatic Ehlers-Danlos, Loeys-Dietz, and Marfan syndromes) are also associated with aneurysms in the proximal aorta, as well as with other vascular and nonvascular

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anomalies and sudden death—often at a young age. Vascular and extravascular disease patterns provide useful clues to diagnosis and prognosis and inform treatment. Progression of enlargement of noninflammatory TAAs has been shown to be diminished by beta-blockers and angiotensin-receptor blockers. Risk of dissection and rupture may also be reduced by avoiding strenuous activities and trauma, especially in young patients wishing to do weightlifting and play contact sports.[9] While these prophylactic measures have proven beneficial in noninflammatory TAAs, they have not been well studied in the setting of inflammation. Nonetheless, it is reasonable, barring any contraindications, to implement interventions that reduce aortic wall pressure in patients with an inflammatory TAA.

The diagnosis of a noninflammatory TAA urges genetic testing of probands and family members. While most patients have positive family histories of similar disease features, some represent spontaneous mutations and family histories may be unrevealing. A subset of people with noninflammatory TAAs lack syndrome-associated features but nonetheless have a 20% chance of having relatives with a TAA (familial TAAs), suggesting a genetic lesion. Identifying such a patient should prompt evaluation of the thoracic aorta in first-degree relatives.[9]

It is critical for the clinician to realize that most noninflammatory TAAs enlarge slowly and are asymptomatic until they become very large. However, inflammatory and genetically determined TAAs associated with matrix anomalies may enlarge much more rapidly. In either case, symptoms such as chest or upper back pain place patients at greatly increased risk of life-threatening thoracic aorta rupture.[9]

In this issue of the *Journal*, Dr. Alison H. Clifford[10] describes a very logical approach to diagnosis and treatment of inflammatory, noninfectious thoracic aortitis. This large subset includes numerous systemic autoimmune diseases, giant cell arteritis, Takayasu arteritis, and immunoglobulin G4-related disease. If none of the foregoing can be proven and the lesion is singular and restricted to the proximal aorta, a provisional diagnosis of clinically isolated aortitis (CIA) is appropriate. It is critical to recognize that the diagnosis of CIA is always made with the proviso that CIA may be an initial presentation of a more serious multifocal or systemic illness. Such knowledge obligates periodic clinical reassessments and imaging of the entire aorta and its primary branches and inquiries that may reveal newly emerging elements of systemic diseases (eg, Takayasu arteritis, giant cell arteritis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, sarcoidosis, Behçet syndrome, or Cogan syndrome).[11]

TAA management requires a multispecialty team. Most rheumatologists are facile in assessment and management of the vasculitides and systemic autoimmune disorders, but cardiologists, cardiothoracic surgeons, and radiologists are essential to assess rates of TAA progression; risk of dissection, rupture, and sudden death; and timing and best type of life-saving surgical intervention. In the absence of a definite diagnosis of thoracic aortic inflammation, genetic consultation is advised to determine whether congenital matrix-associated anomalies are present.

QUESTIONS RAISED AND LESSONS LEARNED

Inflammatory TAAs raise many questions regarding pathogenesis. Studies of numerous autoimmune diseases have identified immune targets in diseases such as myasthenia gravis, Graves disease, type 1 diabetes mellitus, pemphigus, celiac disease, idiopathic membranous nephropathy, neuromyelitis optica, multiple sclerosis, and antibasement membrane (Goodpasture) disease.[12–18] At present, we do not have convincing identification of specific target autoantigens in the walls of large vessels. Molecular identity of antigens would still leave unanswered whether tissue injury occurred because of loss of tolerance to or modification of native antigen (neoantigen). Whether antigens related to recently identified aortic microbiomes play a role in pathogenesis is yet unexplored.[19–21]

We have learned a great deal about the aorta in the past 80 years. One important lesson is that calling this vessel by the same name from its origin to its terminus is misleading. Like other vessels, its characteristics are not fixed throughout its topography or over time. The aorta is an excellent example of structural and physiological adaptation to changes in physical demands and the needs of organs to be perfused. With increasingly sophisticated genetic, molecular, and immunologic research tools, it is almost certain that the fascinating questions raised in this editorial will in time be solved.

DISCLOSURES

Dr. Hoffman has disclosed being an advisor or review panel participant for Genentech.

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