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Insights into Pathogenesis of Takayasu's Arteritis

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Abstract

Takayasu's arteritis (TA) is an idiopathic large vessel inflammatory disease that predominantly affects young women. The pathology includes granulomatous changes. The inflammatory process favors the cervico-cranial vessels of the aortic arch, the thoracic more than the abdominal aorta and produces stenoses 4-5 times more often than aneurysms (Figure 1) [1,2]. Wider global recognition of TA has led to questioning of the accuracy of the long-accepted demographic of an Asian stereotype and the notion that the illness follows a triphasic (systemic, vascular inflammatory and burned out) course. Larger aggregate data has also increased appreciation of persistent disease activity, need for surgical remedies and a greater degree of disability than heretofore recognized. Recent insights into pathogenesis have led to experimental trials of novel therapies. This review will explore these insights and resultant changes in both medical and surgical interventions.

Keywords: Takayasu's arteritis; Large vessel vasculitis; Pathogenesis

Historical Background

The first recognition of TA is most often credited to Mikito Takayasu (1905- Japanese Ophthalmology Society Annual Meeting). However, there are earlier descriptions of TA by G.B. Morgagni and William Savory [3,4]. In 1761 Morgagni described a 40 year old female who lost her radial pulses years before her death. Postmortem findings included subclavian obstruction and severe aortic changes characterized by ectasias, aneurysms and stenosis. In 1856 Savory described a 22 year old female with bruits over the left carotid artery and sternum as well as weak pulses in the femoral arteries. Post-mortem examination revealed the inner layers of the arteries appeared to be thickened and have a 'wrinkled' appearance similar to what is called a 'tree barking' today. He noted that the arteries and not the veins were affected and collateralization can appear around obliterated segments. He reasoned that inflammation was the underlying cause and the disease likely progressed over long periods of time and could be asymptomatic. The detailed and insightful observations noted by both Morgagni and Savory deserve to be remembered.

Epidemiology

Median age at disease onset in most series is 25-30 years. Females are affected at least 8 times more often than males. While much of the literature has emphasized a predilection for Asians, recent reports reflect diverse racial and ethnic populations (e.g. Italy, France, South Africa, Mexico, South America and the United States) and have raised questions about the accuracy of the Asian stereotype. Demographic features of patients and disease manifestations between cohorts can vary considerably. Patients in the US [1,2], Japan [5] and Africa [6] tend to be younger (mean age at diagnosis ~25 years) than patients in Italy and France (mean age at diagnosis ~ 30-40 years) [7,8]. Some investigators do not define TA as a disease of younger individuals and some series include elderly patients. The lack of consensus regarding age as a criterion produces bias in demographic comparisons. Cohorts in Japan, Korea, the United States, France and Italy [2,5,7,8,9] include ~80-90% females; those from India have about 60% females [10]. In Japan almost all patients are Japanese, in the US and Italy patients are predominantly Caucasian.

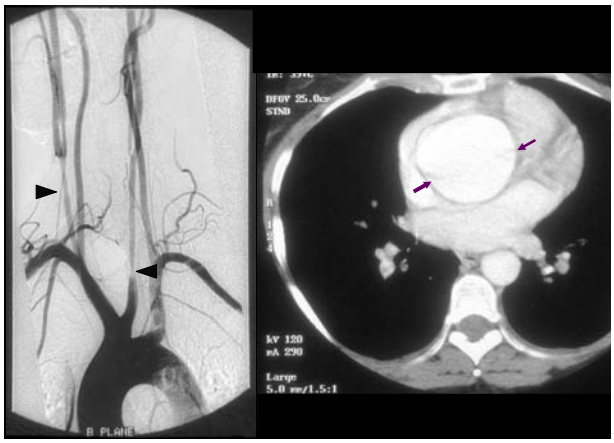

Figure 1: Arterial lesions of Takayasu's: (Left) Interventional angiogram of patient with TA showing stenotic lesions of both common carotid arteries (arrowheads). (Right) MRA/I of chest showing large aneurysmal dilatation of the ascending aorta (arrows).

Morbidity and Mortality

While the five year survival of TA remains favorable (~94%), the disease related morbidity can be devastating. Claudication symptoms are common and affect activities of daily living in 60% of patients. Renal artery stenosis can cause a significant rise in central blood pressure. This is further complicated by the fact that peripheral blood pressure measurements may not accurately reflect central pressures. Carotid and vertebral stenosis can cause lightheadedness, visual changes or even stokes. Vascular interventions including angioplasty and bypass/reconstruction procedures are performed for critical areas of stenosis. However, re-stenosis rates remain high (78% and 36% respectively). This high failure rate may be related to unrecognized active disease at the time of intervention. It is estimated that anywhere from 74-83% of patients become partially of fully disabled [1,2]. Many challenges still remain in the management of this disease.

One challenge to achieving better outcomes is being able to

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differentiate active from remission and 'burned out' disease. Clinical, surrogate serologic and imaging markers are useful but imperfect because of limited sensitivity. Surgical specimens from presumed clinically inactive patients have shown histological features of active disease in up to 44% of cases [2,11].

Pathology

Pathologic manifestations of TA can be broken down into active, acute, chronic and fixed injury [12,13]. The active phase reveals inflammation with granuloma formation and giant cells that are predominately found in the media of large elastic arteries. Zonal necrosis may be seen in the media, often surrounded by giant cells. In the earliest lesions, inflammatory infiltrates are noted in the adventitia, surrounding the vasa vasorum and later extend into the media. The infiltrate is typically composed of lymphocytes, plasma cells and dendritic cells with a varying number of giant cells (Figure 2).

Over time chronic changes start to occur. Fibrosis follows chronic inflammation. There is destruction of the medial elastic smooth muscle layer with replacement with fibrotic tissue. This leads to loss of elasticity of the large vessels. Myointimal proliferation can lead to narrowing or complete occlusion of the lumen. Grossly this gives the intima a tree-bark appearance which is also seen in infectious and other non-infectious causes of aortitis. If the destruction of the acute phase of the disease outpaces the fibrous remodeling, aneurysms may develop. Neovascularization occurs in proportion to thickening of the media. This is thought to be a compensatory adaptation of the vessel as it becomes thickened in order to provide gas exchange and nutrients to the deeper layers of the vessel.

Immunophenotyping of the aortic wall reveals dense aggregates of inflammatory cells in which the central core is compromised of CD20 lymphocytes. Around the periphery are CD3 lymphocytes in close association with S-100 dendritic cells (Figure 3). However, these aggregates are not consistently present in all specimens [14]. This data implies a role for B-cells in the pathogenesis in at least a subset of patients.

Role of Infectious Disease

It is known that as many as 20% of patients have a monophasic course and the disease eventually 'burns out'. However, the majority of patients have a chronic or polyphasic course requiring long term immunosuppressive therapies. The inciting events that cause initiation and those that contribute to disease resolution are unknown. Infectious etiologies have long been suspect.

γ-herpes viruses have been studied in murine models. Because γ-herpes virus 68 (γ-HV68) is homologous to human γ-HV, it has been of special interest. In mouse models, infection with γ-HV68 is known to infect a wide variety of vascular beds; however, it only induces vasculitis in large elastic arteries. Interferon- γ (IFN- γ) plays a major

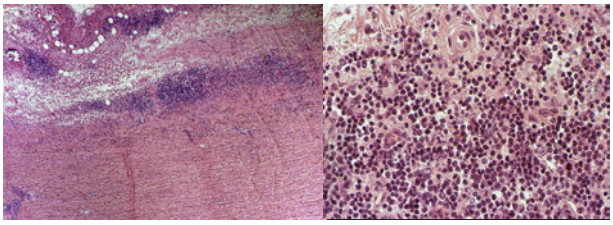

Figure 2: An aortic root aneurysm biopsy reveals mononuclear cells mostly within the adventitia and media. Magnification - Left 10x, Right 400x.

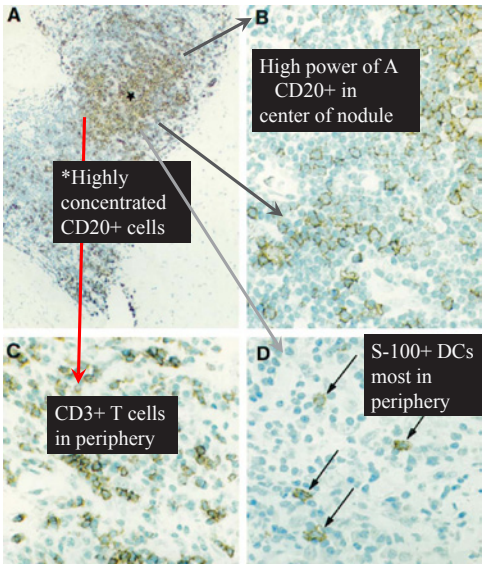

Figure 3: Immunophenotypic analysis of aortic wall cellular infiltrates. CD3 and CD20 cells are most concentrated in adventitia, sometimes forming nodules. When nodules form B-cells aggregate at the core. T-cells and dendritic cells (DCs) are mostly in the periphery. (reference 14)

role in controlling this process as IFN-γ receptor knockout mice and chronically INF-γ depleted mice develop more persistent necrotizing arteritis affecting the aortic root. Interestingly, B-cell deficient mice infected with γ-HV68 also develop aortitis [15,16].

An association between *mycobacterium tuberculosis* (TB) and TA has been suggested based on a higher incidence of positive tuberculin skin tests than seen in controls in Turkish cohorts [17]. In addition, mycobacterium heat shock protein (mHSP)-65 and its human homologue, heat shock protein (hHSP)-60, induce T-cell proliferation (predominately CD4) to a greater degree than noted in healthy controls. Patients also tend to have high levels of IgG anti-mHSP-65 and IgG anti-hHSP-60, supporting a role for B-cells in TA [18,19]. These findings suggest that molecular mimicry may be a factor in TA pathogenesis in at least some patients. However, conclusive evidence linking TB to the etiology of TA does not yet exist. In fact, in one study TA patients had similar rates of latent TB compared to controls, as measured by a serum quantiferon gold assay [17].

There is no definitive evidence of an infectious trigger; however, intriguing evidence continues to emerge. Many agents have the capacity to causearteritis, however, the actual event is rare, implying a need for co-factors, including predisposition of the host.

The Link between the Adaptive and Innate Immune System

Dendritic cells are antigen presenting cells (APCs) which are primarily found in the adventitial-medial boundaries of large arteries. Activation of these APCs by antigen activates lymphocytes in situ or in regional lymph nodes. In studies of normal arteries, dendritic cells have been shown to express toll-like receptors (TLRs) which serve to recognize pathogen-associated or "danger"- associated molecular pattern's (PAMPs and DAMPs) that are unique to microbes and certain non-microbial antigens. Different profiles of TLRs have been identified in different large and medium sized vessels e.g. TLR 2 and 4 are commonly expressed in most large vessels, but TLR 1, 3, 5, 6 and 8 are variably expressed in different large vessel territories (e.g.

temporal vs. subclavian vs. aorta vs. carotid) [20]. Once engaged, different TLRs stimulate unique cytokine signatures which are important in recruitment of the adaptive immune response. For instance, in temporal arteries from healthy donors' stimulation of TLR 4 with lipopolysaccharide, a known TLR 4 ligand, there is up-regulation of the chemokine CCL20. This results in the recruitment of CCR6+CD4 T-cells into the vessel wall causing a panarteritis similar to that seen in large vessel vasculitis [21]. Thus blood vessels are not just conduits of blood flow as was once previously thought. They are active, immunologically equipped structures with components that link adaptive and innate immunity. Differences in TLR profiles are likely to contribute to selective vulnerability to injury and capacity to clear antigens.

Role of Target Tissue

Aortitis may occur as a focal isolated abnormality, unrelated to TA. In this regard, it may be one of the 'single organ vasculitides'. In a retrospective review of all aortic pathology over a period of 20 years about 4% of patients had aortitis which was histologically indistinguishable from TA. About two-thirds of these patients did not have any evidence of an associated systemic disease (e.g. giant cell arteritis, TA or other systemic diseases). The vast majority of patients with focal idiopathic aortitis requiring aortic reconstruction will never demonstrate disease beyond the surgical site [22]. There are unique qualities that differentiate aortic tissue from other vascular sites. Furthermore, aortic segments (root/arch vs. descending and abdominal) differ in gene expression, structural components and vulnerability and response to injury.

The differences start to become apparent during early embryonic development. The greatest part of the arterial tree is derived from mesoderm (Mes). However, a major exception is the smooth muscle cells (SMC) of the aortic arch and the proximal arch vessels. They are derived from neuroectoderm (NEct). In vitro studies on avian embryos have shown important differences between SMC from NEct and Mes origin. NEct derived SMC display a reduced serum requirement for growth. In response to stimulation with TGF-β1, DNA synthesis is increased in NEct derived cells, while growth was inhibited in Mes derived cells. TGF-β receptor expression is similar in NEct and Mes –derived SMC, however, NEct SMC have TGF- β type II receptors that are more highly glycosylated. The exact significance of glycosylation of this receptor is currently unknown [23].

Further differences between the aortic arch and the abdominal aorta can be seen in disease states. Most often microscopy of thoracic arch aneurysms reveals mucoid degeneration, fragmentation of elastic fibers and loss of SMC. This is frequently referred to as 'cystic medial necroses'. Abdominal aortic aneurysms are most often characterized by severe intimal atherosclerosis, chronic transmural inflammation and remodeling of the elastic media. Genetic expression analysis has revealed that there are 200 (out of 1185 genes evaluated) unique genes that differentiate thoracic from abdominal aortic tissue [24]. Furthermore, the aortic arch contains a higher concentration of vasa vasorum then more distal segments of the aorta (Figure 4). These differences suggest the presence of immune and biochemical differences that determine disease vulnerability.

Within the thoracic aorta changes in the structure of the media appear with age. The basic subunit of the media is the elastic lamella which is an individual sheet of elastin, collagen and smooth muscle units. In mammals, elastic lamellas are added to the adventitial side of the media as the vessel grows. Species with adult aortas with 29 or more lamellae develop vasa vasorum that extend into the media as this appears to be the "critical depth" in which filtration from the lumen can provide nutrition (Figure 5). With age the distance between the individual elastin lamella increases. The morphology of the lamella change from a wavy to a more linear pattern. In addition, the proportion of elastin to collagen decreases. The end result is a more rigid vessel [25,26]. Thus, young aortic tissue is clearly different from aged tissue with different predispositions to insult (Table 1).

Takayasu's and Crohn's Disease

TA and Crohn's disease (CD) have been associated more often than expected by chance alone. In a French study of forty-four patients with TA, 4/44 had biopsy-proven CD (9% concordance). Numerous case reports have documented this association as well [27]. Both TA and CD have pathology that includes granuloma formation. CD lesions may also have localized areas of vasculitis. Both diseases can progress in a patchy distribution [28]. These overlapping features suggest a possible enteric abnormality that sets the stage for TA in at least a subset of TA.

Therapeutic Implications

TA has been considered primarily a T-cell mediated disease. The aortic cellular infiltrate in TA has a high concentration of CD4+ (14%), CD8+ (15%) and γδ T lymphocytes (31%) [29]. Peripheral

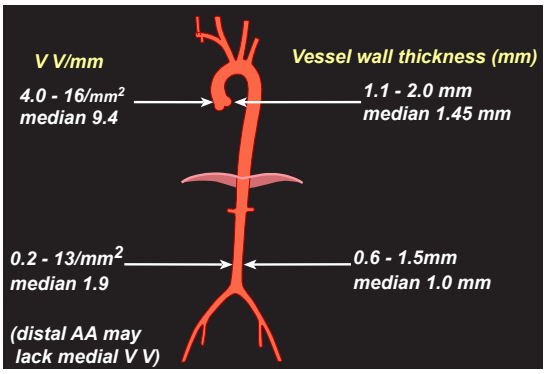

Figure 4: Density of vasa vasora (V V) in the human aorta: The concentration of the vasa vasora is highest in the aortic arch and decreases in more distal segments where the vessel wall becomes thinner.

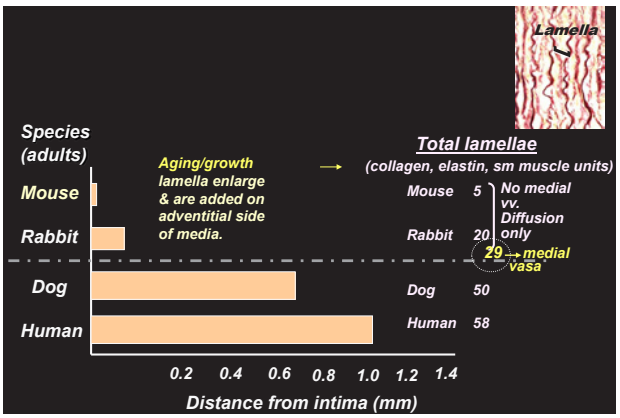

Figure 5: Differences in aortic media between species: The number of lamina (consecutive paired elastic layers) is proportionate to the thickness of the aortic wall. Species with less than 29 lamella units as an adult do not develop vasa vasorum within the media. This is thought to represent the limit to which nutrients and gas exchange can occur from the adventitial V V or the main vessel lumen. (adapted from Reference 25).

	Thoracic aorta (arch)	Abdominal aorta
Wall thickness	greater	
Wall diameter	30-40% greater	
Elastic fiber content	greater (decreases distal from root)	
Derivation of SMCs*	ectoderm	Mesoderm
Vasa vasorum (media)**	numerous	few to absent
Functional differences	greater elasticity	
Disease predilections	inflammatory cystic medial necrosis	more severe atherosclerosis

*SMC –smooth muscle cells **penetration of vasa vasora into medial layer

Table 1: Differences between the thoracic and abdominal aorta.

blood subset analyses reveal high CD4+/CD8+ lymphocyte ratios [30]. Cells with a T helper 1 (Th1) pattern are important in the formation of granulomas through release of IFN-γ and TNF-α. IFN-γ also has an important role in the formation of giant-cells, neovascularization and intimal proliferation [31]. The evidence supporting Th17 cells in the pathogenesis of large vessel vasculitis [32], has led to studies looking at tocilizumab in the treatment of TA as well as giant cell arteritis. Tocilizumab is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor (IL-6R). IL-6 has many important roles including supporting the development of Th17 cells from naïve T-cells and inhibition of differentiation of T-regulatory cells through transforming growth factor-β (TGF-β). Initial studies in treatment of TA have been promising [33], but larger sample sizes will be needed in order to draw definitive conclusions about the relative importance of these pathways.

Inhibition of Th1 response in TA has primarily been limited to studies looking at blockade of TNF-α. A retrospective study of 25 patients with refractory TA treated with TNF inhibitors showed that over a median follow-up of 28 months the majority of patients were able to achieve either a partial or complete remission. Sixty percent of these patients were able to wean completely off steroids [34]. Randomized control trials will be needed to further assess these observations. Blockade of just one cytokine may not be enough to substantially impact the inflammatory cascade in large vessel vasculitis. A multi-targeted approach may also merit consideration. Ustekinumab is one example of a biologic drug which blocks multiple pathways. It was first designed to bind to the p40 subunit of IL-12 and thus target the Th1 pathway. It was subsequently discovered that IL-23 also contains the p40 subunit and thus Ustekinumab also targets the Th17 pathway. Ustekinumab is currently approved for treatment of psoriasis and is in phase two development for psoriatic arthritis and CD [35].

The T-cell dominated perspective of TA has recently been challenged. New evidence supports an important role for B-cells. Inflammatory infiltrates within the adventitia have been shown to have a predominance of both CD3+ and CD20+ cells. B-cells form aggregates with T-cells as well as dendritic cells, suggesting what might be important cross-talk [14]. B cell activating factor (BAFF), important in the survival and differentiation of B lymphocytes, has been shown to correlate with disease activity [36,37]. Additional data has also pointed to anti-aortic endothelial antibodies in playing a role in pathogenesis [19], but this data is more tenuous. In addition, the serum B cell pool in TA patients with active disease includes fewer naïve B cells and higher concentrations of B cell derived plasma blasts. Preliminary data in limited numbers of patients has demonstrated that anti-B cell therapy (rituximab) may be effective in refractory cases of TA [37]. These observations warrant further studies that evaluate B cell directed therapies.

Summary

Management of Takayasu's disease remains a challenge because of an incomplete understanding of pathogenesis, lack of reliable biomarkers of disease activity and limited treatment options. However, recent insights into pathogenesis, an improved understanding of target selectivity and emerging data on the use of biologic agents holds the promise of change for the better.

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