**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, 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.

**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...
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 vasoform 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 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 cause aortitis, 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.

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

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
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.

**Reference**


4. Savory WS (1856) Case of a Young Woman in whom the Arteries of both Upper Extremities and of the Left Side of the Neck were throughout completely Obliterated. Med Chir Trans 39: 205-219.


