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REVIEW ARTICLE

A Review on Pathophysiological Mechanisms, Clinical Heterogeneity, and Management of Takayasu Arteritis

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Abstract: Takayasu arteritis (TA) is a rare, idiopathic, chronic granulomatous vasculitis that predominantly affects the aorta and its primary branches. Often referred to as "pulseless disease," it manifests primarily in women of reproductive age, particularly within Asian populations, although its global footprint is increasingly recognized. The disease course is characteristically biphasic, initiating with a systemic inflammatory phase marked by non-specific constitutional symptoms, followed by a chronic sclerotic phase resulting in vascular stenosis, occlusion, or aneurysm formation. This review discusses about the immunopathogenesis of TA, highlighting the interplay between genetic susceptibility specifically the Human Leukocyte Antigen (HLA) alleles and cell-mediated autoimmunity involving T-cells and macrophages. The clinical spectrum, ranging from silent progression to catastrophic vascular events such as aortic dissection and cerebrovascular ischemia is also discussed in this review. Diagnostic challenges persist due to the frequent dissociation between clinical symptoms and serological markers of inflammation, necessitating a reliance on advanced imaging modalities like Magnetic Resonance Angiography (MRA) and 18F-FDG PET/CT. Moreover, the therapeutic regimen is evolving beyond corticosteroids to include steroid-sparing immunosuppressants and novel biologic agents targeting specific cytokines like IL-6 and TNF-α. This review provides current literature to provide a cohesive understanding of TA, indicating the critical need for early detection and multidisciplinary intervention to mitigate morbidity and mortality.

Keywords: Takayasu arteritis; Large-vessel vasculitis; Granulomatous inflammation; Aortic arch syndrome; Biologic therapy

1. Introduction

Takayasu arteritis (TA) represents a unique entity within the spectrum of large-vessel vasculitides, characterized by a predilection for the aorta and its major branches, including the carotid, subclavian, and renal arteries. First described by the Japanese ophthalmologist Mikito Takayasu in 1908, who observed characteristic retinal arteriovenous anastomoses, the condition has since been defined by its sequelae of vascular insufficiency [1]. Historically termed "pulseless disease" due to the frequent obliteration of radial pulses, TA poses significant diagnostic and therapeutic challenges due to its insidious onset and the heterogeneity of its clinical presentation.

The epidemiology of TA shows a distinct female preponderance, with a female-to-male ratio ranging from 8:1 to 9:1, typically manifesting in the second or third decade of life [2]. While the disease was initially thought to be restricted to East Asian populations, recent epidemiological data indicates a worldwide distribution, albeit with varying genetic associations and clinical phenotypes across different ethnic groups. The etiology remains incompletely understood; however, strong associations with specific HLA alleles, particularly HLA-B*52, suggest a genetic predisposition triggered by yet unidentified environmental or infectious agents [3].

The burden of the disease stems from its progressive nature, where chronic inflammation leads to vessel wall remodeling. This process results in stenosis, occlusion, or aneurysmal dilation, causing end-organ ischemia. The clinical course is often prolonged, necessitating long-term immunosuppression, which contributes to the complexity of patient management. This article provides current literature on the pathophysiology, clinical features, and management strategies for TA, referencing pivotal studies to provide an updated perspective on this complex vasculitis.

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2. Pathophysiology

The pathogenesis of Takayasu arteritis is a multifactorial process driven by cell-mediated immunity, where inflammation targets the arterial wall layers, specifically the media and adventitia.

2.1. Immunopathogenesis

The primary lesion in TA is panarteritis with a granulomatous response. The inflammatory infiltrate is composed chiefly of T lymphocytes, macrophages, and multinucleated giant cells [4]. It is hypothesized that an unknown antigen, potentially a heat shock protein, triggers an immune response in genetically susceptible individuals. This interaction leads to the activation of dendritic cells and the subsequent differentiation of naïve CD4+ T cells into Th1 and Th17 lineages. These effector cells release pro-inflammatory cytokines, including Interferon-gamma (IFN-γ), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α), which perpetuate the inflammatory cascade and recruit additional immune cells to the vascular wall [5].

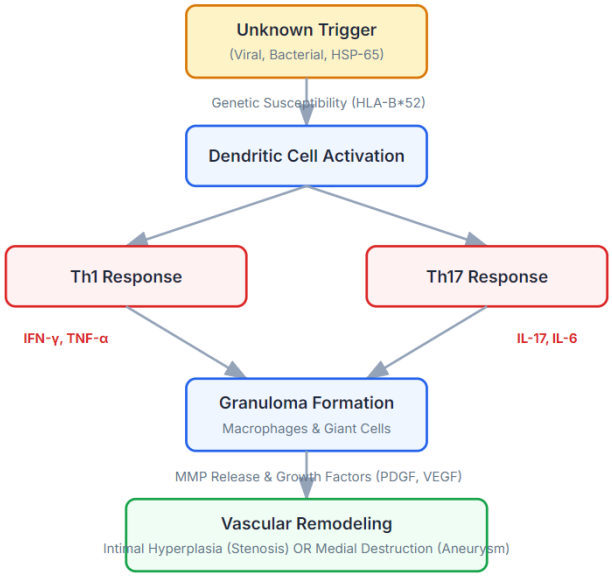

Figure 1. Immunopathogenesis of Takayasu Arteritis

2.2. Vascular Remodeling and Histopathology

The inflammatory milieu activates matrix metalloproteinases (MMPs), enzymes responsible for degrading the elastic lamina and extracellular matrix components. This destruction of the medial layer compromises arterial integrity, predisposing the vessel to dilation and aneurysm formation [6]. Concurrently, the release of growth factors such as Platelet-Derived Growth Factor (PDGF) stimulates the proliferation of myofibroblasts and smooth muscle cells in the intima. This hyperplastic response, termed intimal hyperplasia, leads to concentric thickening of the vessel wall and luminal narrowing, resulting in the characteristic stenotic lesions observed in the late stages of the disease [7]. The vasa vasorum, the small blood vessels supplying the arterial wall, also exhibit severe inflammation and proliferation, contributing to ischemic damage within the vessel wall itself.

3. Clinical Manifestations

The clinical presentation of TA is notoriously variable, often described as evolving through a "triphasic" pattern, although these phases may overlap or be absent in individual patients.

3.1. Systemic Inflammatory Phase

The initial phase, often referred to as the "pre-pulseless" stage, is dominated by non-specific systemic symptoms. Patients frequently report constitutional complaints such as malaise, weight loss, low-grade fever, night sweats, and arthralgia [8]. This prodromal period can last for months or years, and because vascular signs are absent, the diagnosis is frequently missed or misattributed to infections

or other connective tissue disorders. Elevation in acute-phase reactants, such as Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), is common during this stage but is not pathognomonic [9].

Table 1. The Numano Angiographic Classification of Takayasu Arteritis

Type	Vascular Involvement
Type I	Involvement limited to the branches of the aortic arch (carotid, subclavian, vertebral arteries).
Type IIa	Involvement of the ascending aorta, aortic arch, and its branches.
Type IIb	Involvement of the ascending aorta, aortic arch and its branches, and the thoracic descending aorta.
Type III	Involvement of the thoracic descending aorta, abdominal aorta, and/or renal arteries.
Type IV	Involvement of the abdominal aorta and/or renal arteries.
Type V	Combined features of Type IIb and Type IV (involving the entire aorta and its major branches).

Coronary or pulmonary artery involvement should be noted as C(+) or P(+) respectively

3.2. Vascular Occlusive Phase

As the inflammation progresses to fibrosis and stenosis, signs of vascular insufficiency emerge. This constitutes the "pulseless" phase. The specific symptoms depend entirely on the arterial bed involved:

3.2.1. Subclavian and Axillary Arteries

Involvement here leads to arm claudication, coolness of the extremities, and a discrepancy in systolic blood pressure (>10 mmHg) between the arms, a hallmark physical finding [10].

3.2.2. Carotid and Vertebral Arteries

Stenosis in these vessels compromises cerebral perfusion, resulting in dizziness, syncope, visual disturbances (amaurosis fugax), and headaches. Severe carotidynia (pain over the carotid arteries) is a specific sign of active inflammation in the neck vessels.

3.2.3. Aorta and Renal Arteries

Involvement of the abdominal aorta and renal arteries is a major cause of secondary hypertension in young patients. Renal artery stenosis activates the renin-angiotensin-aldosterone system, leading to severe, often refractory hypertension, which further exacerbates cardiovascular risk [11].

3.2.4. Coronary and Pulmonary Arteries

Although less common, coronary ostial stenosis can lead to angina or myocardial infarction. Pulmonary artery involvement may manifest as dyspnea, hemoptysis, or pulmonary hypertension, often complicating the clinical picture [12].

3.3. Clinical Classification

To standardize the description of vascular involvement, the Numano classification system is widely utilized. This system categorizes the disease into types based on the angiographic location of the lesions:

- **Type I:** Branches of the aortic arch.
- **Type IIa:** Ascending aorta, aortic arch, and its branches.
- **Type IIb:** Type IIa plus thoracic descending aorta.
- **Type III:** Thoracic descending aorta, abdominal aorta, and/or renal arteries.
- **Type IV:** Abdominal aorta and/or renal arteries.
- **Type V:** Combined features of Type IIb and IV (involving the entire aorta and its branches) [13].

This topographical classification aids in correlating clinical symptoms with anatomical defects and guides therapeutic planning

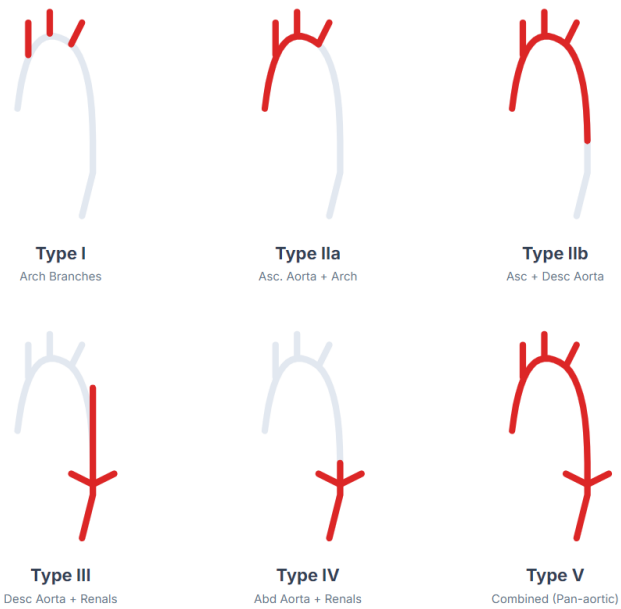

Figure 2. Numano Angiographic Classification

Table 2. Frequency of Clinical Manifestations in Takayasu Arteritis

Clinical Manifestation	Estimated Frequency (%)	Pathophysiological Basis
Limb Claudication	30% – 60%	Stenosis of subclavian, axillary, or iliac arteries causing muscle ischemia.
Constitutional Symptoms	50% – 70%	Systemic cytokine release (IL-6, TNF-α) during the active inflammatory phase.
Hypertension	33% – 76%	Renal artery stenosis or loss of aortic elasticity.
Pulse Deficits	50% – 85%	Occlusion of radial, ulnar, or brachial arteries ("Pulseless disease").
Carotidynia	10% – 30%	Active inflammation of the carotid sheath.
Visual Disturbances	10% – 20%	Retinal ischemia due to carotid stenosis (hypoperfusion retinopathy).
Aortic Regurgitation	20% – 25%	Dilation of the ascending aorta and aortic root.

4. Diagnosis

The diagnosis of Takayasu arteritis is complex due to the absence of a single gold-standard test. It relies on a combination of clinical features, inflammatory markers, and characteristic imaging findings.

4.1. Diagnostic Criteria

The American College of Rheumatology (ACR) criteria (1990) are commonly used for classification, requiring at least three of the following six criteria: age of onset <40 years, claudication of extremities, decreased brachial artery pulse, blood pressure difference >10 mmHg between arms, subclavian or aortic bruit, and angiographic abnormalities [14]. While useful for research, these criteria may lack sensitivity for early-stage disease.

4.2. Imaging

Imaging plays a pivotal role in diagnosis and monitoring disease activity.

- **Conventional Angiography:** Historically the standard, it delineates luminal anatomy, showing stenosis, occlusion, and collateral circulation. However, it is invasive and exposes patients to radiation.
- **CT Angiography (CTA):** CTA provides high-resolution images of the vessel lumen and wall. It helps in assessing wall thickening, which is an early sign of inflammation preceding stenosis [15].

- **Magnetic Resonance Angiography (MRA):** MRA is increasingly preferred, particularly for young patients requiring serial monitoring, due to the lack of ionizing radiation. It excels at visualizing vessel wall edema and thickening, offering functional insights into active inflammation [16].
- **18F-FDG PET/CT:** Positron Emission Tomography (PET) integrated with CT is highly sensitive for detecting metabolic activity in the vessel wall. It is particularly valuable in identifying active disease in patients with normal inflammatory markers and for assessing response to therapy [17]

Table 3. American College of Rheumatology (ACR) 1990 Criteria for Classification

Criterion	Definition
Age at onset ≤40 years	Development of symptoms or findings related to Takayasu arteritis at age ≤40.
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremities while in use.
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries.
BP difference >10 mmHg	Difference of >10 mmHg in systolic blood pressure between arms.
Bruit over subclavian/aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta.
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes.

Table 4. Imaging Techniques used for Diagnosis of Takayasu Arteritis

Modality	Advantages	Limitations	Utility
Doppler Ultrasound	Non-invasive, low cost, assesses wall thickness in carotids ("Macaroni sign").	Operator dependent; poor visualization of thoracic aorta.	Initial screening for carotid/subclavian involvement.
CT Angiography (CTA)	High resolution of lumen and wall; widely available; rapid acquisition.	Radiation exposure; iodinated contrast risks (nephrotoxicity).	Detailed anatomical mapping prior to surgery.
MR Angiography (MRA)	No radiation; excellent soft-tissue contrast (wall edema vs. fibrosis).	High cost; longer scan time; contraindicated in some implants.	Preferred for serial monitoring in young patients.
18F-FDG PET/CT	Functional imaging; detects active inflammation (metabolic activity) before structural changes.	High radiation dose; cost; availability; false positives in atherosclerosis.	Differentiating active disease from fibrotic scars.

5. Therapeutic Management

The management of TA aims to suppress systemic inflammation, prevent vascular progression, and manage ischemic complications.

5.1. Medical Therapy

Glucocorticoids remain the cornerstone of initial therapy. High-dose prednisolone (0.5–1 mg/kg/day) is typically initiated to induce remission. However, monotherapy often fails to sustain remission or results in steroid toxicity upon tapering. Consequently, steroid-sparing immunosuppressive agents are introduced early. Methotrexate and azathioprine are frequently used first-line adjunctive therapies [18]. Mycophenolate mofetil and leflunomide are alternatives for intolerant patients or resistant cases. In refractory disease, biologic agents have revolutionized management. Tocilizumab, an IL-6 receptor antagonist, has shown significant efficacy in reducing disease activity and sparing steroids [19]. Tumor Necrosis Factor (TNF) inhibitors, such as infliximab and adalimumab, are also effective, particularly in patients with persistent vascular inflammation [20]

5.2. Surgical and Interventional Management

Revascularization is indicated for severe stenotic lesions causing critical ischemia, uncontrolled renovascular hypertension, or enlarging aneurysms. Options include Endovascular Therapy (EVT) with percutaneous transluminal angioplasty (PTA) and stenting, or open surgical bypass. It is imperative that interventions are performed during the quiescent phase of the disease, as procedures performed during active inflammation have high rates of restenosis and failure [21].

Table 5. Pharmacological Management

Drug Class	Agent(s)	Role in Therapy	Mechanism of Action
Glucocorticoids	Prednisolone	First-line induction	Broad anti-inflammatory; rapid suppression of cytokines.
Conventional DMARDs	Methotrexate, Azathioprine, Mycophenolate Mofetil	First-line maintenance / Steroid-sparing	Inhibits purine/pyrimidine synthesis; suppresses T/B cell proliferation.
IL-6 Receptor Antagonists	Tocilizumab	Refractory disease	Blocks IL-6 signaling; highly effective for systemic symptoms.
TNF-α Inhibitors	Infliximab, Adalimumab	Refractory disease	Neutralizes TNF-α; useful in granulomatous inflammation.
JAK Inhibitors	Tofacitinib, Baricitinib	Experimental / Refractory	Inhibits JAK-STAT pathway; suppresses multiple cytokines.

5.3. Complications and Prognosis

The morbidity in TA is substantial. Beyond the classic ischemic symptoms, patients may develop severe complications such as aortic regurgitation due to dilation of the aortic root, leading to congestive heart failure. Retinopathy, secondary to carotid hypoperfusion, can threaten vision [22]. Rare but life-threatening complications include aortic dissection and rupture of aneurysms. Cardiac involvement may also manifest as myocarditis or pericarditis. The prognosis varies; while the mortality rate has decreased with modern therapy, the "burnt-out" phase often leaves patients with permanent vascular deficits requiring lifelong management. Research is increasingly focusing on the molecular basis of TA to identify more specific therapeutic targets. The role of Janus Kinase (JAK) inhibitors, such as tofacitinib, is currently being explored for refractory cases, showing promising preliminary results [23]. Furthermore, the identification of reliable serum biomarkers that correlate better with mural inflammation than CRP or ESR is a critical unmet need. Personalized medicine approaches, utilizing genetic profiling to predict response to specific biologics, represent the future of TA management.

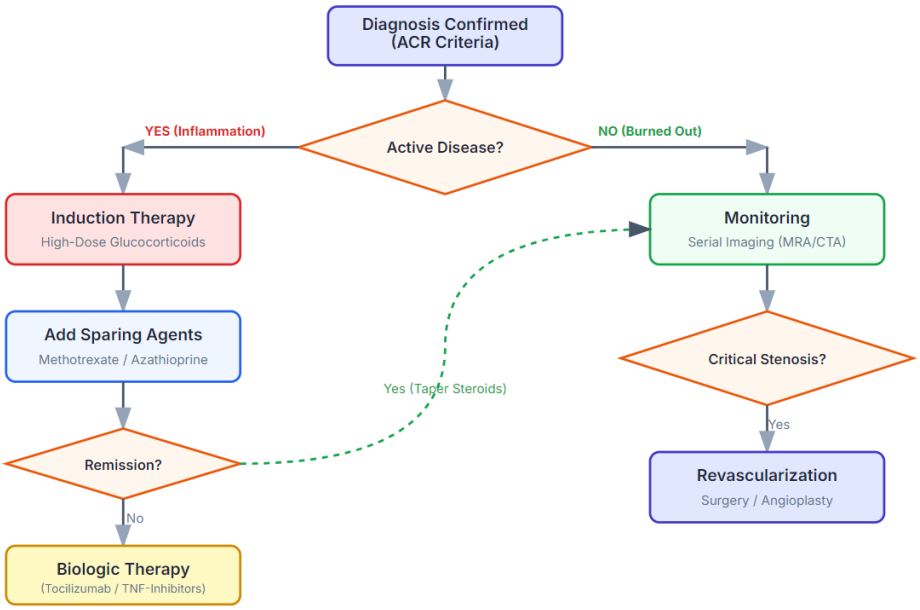

Figure 3. Clinical Management Algorithm

6. Conclusion

Takayasu arteritis is a heterogeneous large-vessel vasculitis that requires a high index of suspicion for early diagnosis. The transition from the non-specific inflammatory phase to the fibrotic pulseless phase represents a critical window for therapeutic intervention. While corticosteroids and immunosuppressants form the backbone of treatment, the advent of biologic therapies offers new hope for patients with refractory disease. Management should be multidisciplinary, involving rheumatologists, vascular surgeons, and radiologists, to optimize outcomes. Future research into the immunogenetic underpinnings of the disease is essential to develop targeted therapies that can halt vascular remodeling and preserve organ function.

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