The large vessel vasculitides can be classified based on many factors, including size of affected vessels, distribution of vessels affected, histopathologic differences, genetic factors, and age at presentation. Giant cell arteritis (GCA) and Takayasu's arteritis (TkA) are the two main medium to large vessel vasculitides. These vasculitides are associated with different racial predilections, vascular distributions, age groups, diagnostic criteria, and treatments. Nevertheless, the many shared histopathologic features, genetic factors, and overlap in presentation of these two diseases suggest that they may actually be variable presentations of the same disease process, i.e., large vessel vasculitis. This article will review the genetics, histopathology, disease mechanisms, and diagnostic criteria for both TkA and GCA. Overall, despite major advances in our understanding of these two diseases, it is still debated whether these two large vessel vasculitides represent two distinct disease processes or simply variations of the same disease.

**Keywords:** Giant cell arteritis, large vessel vasculitis, pulseless disease, Takayasu's arteritis, temporal arteritis, temporal artery biopsy

**Abstract:**

There are multiple vasculitides which can be classified based on many factors, including size (e.g., small, medium, large) and location (e.g., internal or external carotid distribution) of affected vessels, underlying etiology, association with systemic diseases, predilection for specific organs, genetic factors, and histopathologic findings. The large vessel vasculitides are classified based on the fact that the aorta and its direct branches are frequently affected, with the most common signs and symptoms attributed to vasculitis of these large vessels. Medium and small vessels are frequently affected in large vessel vasculitides and are sometimes the predominant vessels affected, though the presence of large vessel involvement is considered diagnostic of a large vessel vasculitis. The two most common large vessel vasculitides are giant cell arteritis (GCA) and Takayasu arteritis (TkA), both of which are generally characterized by granulomatous inflammation. These diseases are often associated with different age groups (<40 years old for TkA vs. >50 years old for GCA) and have a different incidence across races (TkA with a higher incidence in Asians, whereas GCA has a higher incidence in Caucasians). GCA is frequently associated with vasculitic complications of branches of the external carotid artery, while TkA more frequently affects the aorta and its branches. Although age is a significant differentiating feature, there is significant overlap between these two vasculitic diseases, and there is some debate as to whether TkA and GCA are two distinct clinical entities or simply lie along the spectrum of the same underlying disease process. Nevertheless, these diseases are classified as distinct entities by the American College of Rheumatology (ACR) 1990 criteria and by the 2012 Chapel Hill Consensus Conference (CHCC) criteria. According to the 2012 CHCC on the Nomenclature of Systemic Vasculitides, “the
major discriminator between Takayasu arteritis (TA) and GCA is the age of the patient.\textsuperscript{23} For the ACR criteria, age is a criterion for both TkA and GCA, though it is not required to meet the diagnostic criteria of either disease. Thus, depending on how these diseases are classified, they can be conceptualized as either two distinct vasculitides which have a predilection for different age groups or as variations of the same disease, i.e., large vessel vasculitis.\textsuperscript{9,24}

}\textbf{LABORATORY MARKERS}\n
Despite advances in the understanding of the pathogenesis of large vessel vasculitides, there is no known antibody or specific laboratory test that is diagnostic for either of these diseases. Instead, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) remain the primary biomarkers used for monitoring disease activity in both GCA and TkA. For GCA, elevated ESR >50 mm/h is one of the five diagnostic ACR criteria, while no such laboratory criterion is present in the ACR criteria for TkA.\textsuperscript{15,10} For GCA, decline in acute phase reactants (particularly ESR) is used to monitor disease therapy.\textsuperscript{15,46} One recent study by Kermani et al. demonstrated roughly 84% and 87% sensitivity of ESR and CRP, respectively, for predicting a positive temporal artery biopsy (TAB).\textsuperscript{199}

While acute phase reactants are frequently monitored in TkA, they are likely less reliable than in GCA, though elevated ESR and CRP are associated with active disease and longer time for disease remission.\textsuperscript{47} In a study by Kerr et al., ESR was elevated in 72% of TkA patients with clinically active disease and in 56% of TkA patients in remission, suggesting the ESR is an unreliable indicator for identifying patients with active TkA or identifying patients in remission.\textsuperscript{48} Thus, the elevations in acute phase reactants (particularly ESR) are more closely associated with GCA than TkA and are more reliable in GCA, though normal values certainly do not exclude either diagnosis.

}\textbf{PATHOPHYSIOLOGY}\n
The pathophysiology underlying GCA and TkA shares many similarities, though a few key differences are known. In GCA, dendritic cells in the vessel wall are exposed to a currently unknown antigen. Human leukocyte antigen (HLA) class II interactions with CD4+ T cells lead to downstream TH1 and TH17 CD4+ cell activation and release of inflammatory cytokines (e.g., interleukins [IL-1] and IL-17, respectively). Macrophages are recruited to the areas of inflammation, particularly in the intimal layer of the blood vessels, resulting in vessel fibrosis, followed by stenosis, and eventually occlusion of the vessel.\textsuperscript{199}

Similar to GCA, TkA is presumed to develop from an immune response to an unknown antigen or stimulus, which results in overexpression of heat shock protein 65.\textsuperscript{199} The activation of CD8+ T cells results in the release of perforin and pro-inflammatory cytokines, resulting in inflammation of the vessels. Such as GCA, TH1, and TH17 cells are ultimately activated, resulting in granulomatous inflammation.\textsuperscript{199}

As noted below, TkA is generally more closely associated with certain MHC class I haplotypes, while GCA is more commonly associated with MHC class II haplotypes. Because MHC class I is associated with CD8+ T-cell activation and MHC class II is associated with CD4+ T-cell activation, these genetic findings correlate with the differences in the pathogenesis of each of these diseases. Nevertheless, despite differences in the initial activation of the inflammatory pathway, there appears to be a final common pathway in both GCA and TkA.\textsuperscript{199}

}\textbf{GENETIC ASSOCIATIONS}\n
Both TkA and GCA are T-cell mediated, antigen-driven vasculitides characterized predominantly by activation of both Th1 and Th17 T cells.\textsuperscript{30,31} For both diseases, the presumed underlying antigen remains unknown, and it is believed that the development of both TkA and GCA is dependent on both genetic and environmental factors.\textsuperscript{30,31}

As advances in genetics occur, many diseases have been re-classified based on the underlying genes associated with the disease entities. Many genetic studies have searched for associations between various HLA classes between TkA and GCA. Interestingly, many such studies have found linkages between TkA and MHC class I (HLA-A, HLA-B, and HLA-C) haplotypes, with the HLA-B*52:01 and HLA-Cw*12:02 haplotypes demonstrating genome-wide significant associations.\textsuperscript{25–27} On the other hand, GCA appears to be associated with various MHC class II (HLA-DR, HLA-DQ, and HLA-DR) haplotypes, including various HLA-DRB1*04 alleles.\textsuperscript{28,29}

Prior studies have demonstrated an association between a single-nucleotide polymorphism (SNP) within the IL12B gene and the development of TkA.\textsuperscript{33} This particular gene encodes a shared subunit of both interleukin IL-12 and IL-23. Carmona et al. analyzed genotyping data to determine whether any SNPs predisposed to either TkA or GCA and found that both TkA and GCA were associated with this IL12B gene; however, this was the only non-HLA polymorphism that reached statistical significance in the study.\textsuperscript{122}

Thus, from a genetic perspective, HLA genotyping suggests that GCA and TkA are likely to separate entities, while the currently known SNP shared by both diseases suggests the possibility of a common underlying genetic etiology. Environmental factors are believed to play a role in the development of both diseases, though genetic factors alone do not appear to predict which individuals will develop either disease.

}\textbf{HISTOPATHOLOGIC FINDINGS}\n
Despite their frequent classification as two separate disease processes, GCA and TkA have remarkably similar histopathologic features. The TAB is often viewed as the gold standard for the diagnosis of GCA. Biopsies for GCA are not always definitively “positive” or “negative” since there are many subtleties to differentiate them histologically. However,
findings that are suggestive of a positive TAB include the presence of giant cells and other inflammatory cells (e.g., lymphocytes, epithelioid cells, plasma cells, fibroblasts, and eosinophils), transmural inflammation, occlusion of lumen, and necrosis of the vessel wall. The internal elastic lamina is generally fragmented, reduplicated, or partially absent [Figure 1].

Interestingly, there appears to be a significant overlap between these biopsy findings from GCA patients versus biopsy findings in TkA patients. Morrissey et al. reported a case of TkA in a 17-year-old female patient who underwent endovascular biopsy of the infrarenal aorta, which demonstrated disruption of the internal elastic lamina, giant cells, inflammatory changes, and a thickened intima. Singh et al. performed an aortic biopsy in a TkA patient during aortic angioplasty, which demonstrated fibrocollagenous tissue with multiple fibroblasts, neutrophils, and plasma cells. Yamada et al. examined the histopathology of autopsy specimens from patients with TkA, with a thoracic aorta and intrapulmonary artery specimens demonstrating intimal thickening and fibrosis and disruption of elastic fibers in the media.

Despite many histopathologic similarities between GCA and TkA, there are a few features that distinguish these two diseases. According to Stone et al., GCA tends to involve the inner media more frequently than the outer media and adventitial layers, while the opposite pattern is observed in TkA. While epithelioid histiocytes and giant cells are also seen in both diseases, the presence of compact, well-formed granulomas is more characteristic of TkA than GCA. Stone et al. also noted that aortic wall thickness is often greater in TkA than GCA; however, it is also mentioned that clinical correlation may be required to distinguish these two diseases.

Unlike GCA, vessel biopsies are not routinely performed to diagnose TkA. Furthermore, biopsy specimens are typically from the aorta or other medium to large vessels of the abdomen and thorax. Thus, there is an absence of temporal artery biopsies in the literature for patients diagnosed with TkA. Nevertheless, the similarities in the histopathology for temporal artery biopsies and biopsies from other sites in TkA patients suggest an underlying unifying disease process. Thus, the interpretation of a biopsy specimen as either being consistent with TkA versus GCA is likely determined by the clinical context, including the patient’s age at presentation, signs/symptoms of the patient, and specific vessels affected, rather than a characteristic histopathologic difference.

**Age at Diagnosis**

As previously mentioned, both the CHCC criteria and ACR criteria use age as a distinguishing feature of GCA versus TkA. According to the 2012 CHCC, “the major discriminator between TA (Takayasu arteritis) and GCA is the age of the patient.”

One interesting implication resulting from the diagnostic criteria for GCA and TkA by the ACR is that there is no large vessel vasculitis that frequently encompasses patients in the 40–50 years old age range. The diagnosis of GCA by the ACR requires that 3 of 5 criteria be met, one of which is age of at least 50; however, the diagnosis of GCA is very rarely given to patients below 50. On the other hand, the ACR criteria used to require age <40 for the diagnosis of TA; however, this mandatory criterion was previously removed. However, age <40 is one of six criteria for diagnosis of TkA, for which three must be met for a TkA diagnosis by ACR criteria. Thus, prior to the removal of the mandatory ACR age criteria for Takayasu arteritis of age <40, there was no medium to large vessel vasculitis that applied to patients between 40 and 50 years of age.

Thus, for patients in the 40–50 years of age range, it may be difficult to distinguish whether they represent an older presentation of TkA versus a younger presentation of GCA. In addition, many patients >50 with biopsy-confirmed GCA

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**Figure 1**: (a) Low magnification view of a medium size, temporal, artery in cross-sections. Notice that the changes are more evident in the inner portions of the artery (internal elastic lamina and intima). There is marked intimal hyperplasia occluding the lumen. There are also eosinophilic areas (pink) of intimal necrosis adjacent to the internal elastic lamina. In the region of the internal elastic lamina there is also heavy inflammatory infiltrate. The media (muscularis) is thinned and the adventitia almost free of inflammation (H and E × 1.25). (b) Close up view of the area of the internal elastic lamina (*) that is fragmented and segmentally absent and associated with the multinucleated giant cells and epithelioid histiocytes. The intima (i) is thickened and the media (m) is mildly infiltrated by lymphocytes (H and E, ×20). (c) The multinucleated giant cells (mngc) are adjacent to the elastic lamina fragments and focally engulfed the lamina at the inferior end (H and E × 100 under oil).
who present with pulseless disease of their extremities would also meet the criteria of TkA. Because such patients would meet the diagnostic criteria of both TkA and GCA, it can be debated how to specifically classify such patients, even if the 2012 CHCC consensus may recommend using age as the determining factor.

**Pulseless Disease**

Pulseless disease in younger patients is generally attributed to TkA, while pulseless disease in elderly patients is frequently diagnosed as GCA. Shibutani et al. described a 75-year-old female patient with right upper extremity pulselessness who was noted to have elevated ESR and palpable temporal arteries bilaterally. A biopsy was performed of her brachial artery, demonstrating narrowing of the lumen with multinucleated giant cells, and she was diagnosed with GCA. Her findings met the ACR criteria for GCA. At the same time, in addition to the aforementioned pulselessness, she also had a systolic blood pressure of 40 mmHg in her right arm and selective digital subtraction angiography demonstrating right brachial artery stenosis. Thus, she also met the ACR diagnostic criteria for TkA.

Similar cases of upper and/or lower extremity pulselessness in patients 50 or older have also been documented in the literature, including cases of a 50-year-old male with decreased bilateral ulnar, bilateral pedal, and right radial pulse and a 68-year-old female with bilaterally absent upper extremity pulses. These patients underwent temporal artery biopsies, with findings suggestive of GCA. The former patient exhibited an epigastric bruit but normal aortic angiogram, including the aortic arch, while the blood pressure could not be recorded in the latter. If such findings, including blood pressure difference between each arm and the arteriogram in the latter patients were performed, these patients would have likely met the current ACR criteria for TkA in addition to GCA. Therefore, many older patients (>50) with pulseless disease likely meet the diagnostic criteria for both GCA and TkA, and it is debatable whether these patients are an older presentation of TkA versus a less common presentation of GCA.

**Artery Involvement**

GCA can present with different vascular distributions affected, namely cranial artery involvement (i.e., branches of the external carotid artery) versus large vessel involvement (i.e., the aortic arch and its branches). In a 1999 study by Brack et al., patients with large-vessel GCA versus cranial GCA were generally younger (average age 66 vs. 72), had a smaller proportion of females (78% versus 88%), and were more likely to have a negative TAB, with 42% of such patients exhibiting a negative biopsy versus 0% of the cranial GCA patients. Furthermore, patients with large-vessel GCA frequently exhibited arm claudication (78%), arterial bruits (80%), diminished or not palpable pulses (68% and 17%, respectively), decreased blood pressure compared with the contralateral side (58%), and not measurable blood pressure (15%).

Muratore et al. examined patients with radiographically diagnosed large vessel versus cranial GCA and noted that patients with large-vessel GCA were also younger, had more frequent relapses, required longer treatments, and had higher cumulative steroid doses. In this study, only 39% of large vessel GCA versus 95% of cranial GCA met ACR criteria for GCA diagnosis. The features of large vessel GCA thus overlap significantly with features of TkA and could perhaps represent a distinct entity from cranial GCA or perhaps an overlap syndrome with TkA. Given the younger age of onset of large-vessel GCA and the greater similarity to TkA, perhaps such patients actually represent an older age of presentation of TkA.

The presence of aortitis is well known for TkA and likely underdiagnosed for GCA patients. Whereas GCA has many severe complications, including permanent vision loss, complications of aortitis from GCA can lead to aortic aneurysms, aortic dissections, and even death. According to Nuenninhoff et al., out of 168 patients diagnosed with GCA in a 50-year period of time, 27% displayed a large artery complication, and 18% exhibited aortic dissection and/or aortic aneurysm. Other studies with shorter follow-up periods have demonstrated similar incidences of up to 11% for thoracic aortic aneurysm, 10% for abdominal aortic aneurysm, and 14% for large vessel stenosis (particularly the upper limbs). These findings emphasize that there is a significant overlap in the vascular distributions of both TkA and GCA.

**Treatments**

The treatments of both TkA and GCA are quite similar, consistent with a similar underlying disease etiology. Both diseases were historically treated with steroids, though with significant associated morbidity due to steroid-related side effects. Although steroids remain an important treatment in both diseases, steroid-sparing agents such as the IL-6 receptor inhibitor tocilizumab and the dihydrofolate reductase inhibitor methotrexate have reduced the reliance on long-term glucocorticoid therapy. In a single-institution cohort study by Koster et al., patients with GCA who were started on methotrexate in addition to glucocorticoids compared to glucocorticoids alone were roughly half as likely to have disease relapse. Similar findings have been noted in TkA patients, for which glucocorticoids alone failed to prevent relapses in roughly half of the patients, while low-dose methotrexate helped decrease disease recurrence.

Similarly, patients with GCA who were started on tocilizumab in addition to a prednisone taper were less likely to relapse as compared to those who were treated with a 26-week or 52-week taper of prednisone plus a placebo. A similar trial was performed by Nakaoka et al., which examined time to relapse for patients with TkA who were started on a steroid taper plus tocilizumab versus steroid taper plus placebo and noted that time to relapse was higher in patients who were treated with tocilizumab. Although this study did not meet...
Table 1: Characteristics of giant cell arteritis versus Takayasu’s arteritis

|                      | GCA                                      | TkA                                      |
|----------------------|------------------------------------------|------------------------------------------|
| Age association (years old) | >50                                      | <40                                      |
| Arterial distribution | Cranial >extracranial                     | Extracranial >cranial                    |
| Race predilection     | Highest incidence in Caucasians           | Highest incidence in East Asians         |
| Arterial layers affected | Inner media >outer media/adventitia      | Outer media/adventitia >inner media      |
| Primary MHC subtype   | MHC II                                   | MHC I                                    |
| T-cell activation     | CD4+ → Th1 and Th17                      | CD8+ → Th1 and Th17                     |
| Granulomatous inflammation | +++                               | +++                                      |
| Elevated acute phase reactants | +++                              | +                                         |
| Pulselessness         | +                                        | +++                                      |
| Response to glucocorticoids | +++                               | +++                                      |
| Response to TNF inhibitors | +                                | +++                                      |
| Response to IL-6 inhibitors | +++                               | +                                        |

TkA: Takayasu’s arteritis, GCA: Giant cell arteritis, TNF: Tumour necrosis factor, IL-6: Interleukin-6, MHC: Major Histocompatibility Complex, -: No effect/association, +: Minimal effect/association, +++: Significant effect/association.

In summary, both TkA and GCA are primarily large vessel vasculitides which were classically associated with younger (<40 years of age) and older (>50 years of age) patients, respectively. These disease processes have significant overlap in regards to their clinical presentations, laboratory markers, histopathologic findings, and treatments. A summary comparing and contrasting both TkA and GCA is shown in Table 1. Genetic testing has yielded differences in regards to associated HLA haplotypes, though both diseases share at least one common SNP. Both diseases are T-cell mediated in response to a currently unknown antigen, resulting in granulomatous inflammation, with overlapping vascular distributions affected. Although these diseases have been classically viewed as two separate clinical entities with distinct clinical criteria, perhaps they are both two variable presentations of the same disease process. Regardless of the classification of these diseases, ophthalmologists should be aware of the significant overlap between TkA and GCA.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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