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Patterns of Arterial Disease in Takayasu's Arteritis and Giant Cell Arteritis

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Abstract

Objective—To identify and validate, using computer-driven methods, patterns of arterial disease in Takayasu's arteritis (TAK) and giant cell arteritis (GCA).

Methods—Patients with TAK or GCA were studied from the Diagnostic and Classification Criteria for Vasculitis (DCVAS) cohort and a combined North American (NA) cohort. Case inclusion required evidence of large-vessel involvement, defined as stenosis, occlusion, or aneurysm by angiography/ultrasonography, or increased FDG uptake by positron-emission tomography (PET) in at least one of 11 specified arterial territories. K-means cluster analysis identified groups of patients based on pattern of arterial involvement. Cluster groups were identified in the DCVAS cohort and independently validated in the NA cohort.

Results—A total of 1,068 patients were included (DCVAS: TAK=461, GCA=217; NA: TAK=225, GCA=165). Six distinct clusters of patients were identified in DCVAS and validated in the NA cohort. Patients with TAK were more likely to have disease in the abdominal vasculature, bilateral disease of the subclavian and carotid arteries, or focal disease limited to the left subclavian artery than GCA ($p<0.01$). Patients with GCA were more likely to have diffuse disease, involvement of bilateral axillary/subclavian arteries, or minimal disease without a definable pattern than TAK ($p<0.01$). Patients with TAK were more likely to have damage by angiography, and patients with GCA were more likely to have arterial FDG-uptake by PET without associated vascular damage.

Conclusion—Arterial patterns of disease highlight both shared and divergent vascular patterns between TAK and GCA and should be incorporated into classification criteria for large-vessel vasculitis.

Keywords

vasculitis; large-vessel vasculitis; Takayasu's arteritis; giant cell arteritis; angiography

Takayasu's arteritis (TAK) and giant cell arteritis (GCA) are two forms of large-vessel vasculitis (LVV) characterized by immune-mediated inflammation of the large arteries. Classic presentations of TAK and GCA are easily distinguished based on differences in age of onset and presenting clinical features. Historically, GCA was thought to be limited to the cranial arteries, and the distinction between TAK and GCA has been based heavily on cranial symptoms and age at disease onset. However, a large percentage of patients with GCA also have involvement of the extra-cranial arteries with estimates ranging from 20–67% by angiography, 83% by 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, and 100% by autopsy (1–4).

The high prevalence of large-vessel involvement in GCA has led to speculation that TAK and GCA may exist on a single disease spectrum (5–7). Previous studies using hierarchical agglomerative partitioning have shown that large-vessel involvement within an individual

patient is similar for TAK and GCA, as arterial disease in both diseases tends to be contiguous in the aorta and symmetric in paired arteries (8–10). The histopathology of affected arteries is nearly indistinguishable between the conditions (2, 3). However, when clinical analyses are restricted to TAK and large-vessel GCA, differences remain in the age of onset, ethnicity, and clinical presentation (11). Subtle differences have also been shown in the prevalence of specific arterial territory involvement including a higher prevalence of axillary disease in GCA and mesenteric disease in TAK (6, 9, 11, 12). Further exploration into arterial patterns of disease could help refine the argument to what extent TAK and GCA are anatomically distinct disease entities.

The objective of this study was to use unsupervised computer-driven approaches to identify similarities and differences in global patterns of arterial involvement between patients with TAK and GCA using vascular imaging data collected in several large, international cohorts in LVV.

PATIENTS AND METHODS

Study Populations across Four Independent Cohorts:

The Diagnostic and Classification Criteria in Vasculitis (DCVAS) is an international, prospective, observational cohort of patients with vasculitis (13, 14). Comprehensive demographic, clinical, and vascular-imaging data were collected using standardized forms. To be eligible, patients had to be enrolled less than five years since time of diagnosis and only imaging abnormalities present by time of diagnosis were recorded. Patients with TAK or GCA within DCVAS were only included in this study if there was imaging-based evidence of vasculitis in the aorta or branch arteries by angiography, ultrasonography, or FDG-PET and a diagnosis confirmed by expert panel review.

The North American (NA) cohort consisted of patients selected from three independent prospective, observational cohorts: the National Institutes of Health (NIH), the Vasculitis Clinical Research Consortium (VCRC), and the Cleveland Clinic Foundation (CCF). In the NIH cohort patients were recruited between 2014 and 2018 to undergo whole-body angiographic and FDG-PET imaging per a standardized imaging protocol ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02257866) identifier: NCT02257866). In the VCRC cohort, patients with TAK or GCA were recruited from eight centers into a longitudinal observational study from 2006 to 2017. The CCF cohort consisted of patients with TAK or GCA who were under the care of a single investigator from 1992 to 2006. In the NA cohorts, all patients with TAK fulfilled the 1990 American College of Rheumatology (ACR) criteria for the classification of TAK (15). Patients with GCA were included in this study if they had evidence of vasculitis in the aorta or primary branches by angiography or FDG-PET and were either 50 years or older at disease onset or fulfilled the 1990 ACR criteria for the classification of GCA (16). Patients could be enrolled at any point in the disease course. Since many of the VCRC centers participated in the DCVAS study, patients enrolled in both the VCRC cohort and DCVAS cohort were included only in the VCRC cohort.

Imaging data:

Angiographic assessment was performed in patients within the DCVAS cohort at the discretion of the physician and in all patients in the NA cohort using either catheter-based, magnetic resonance, or computed tomographic angiography. Ultrasonography of the large arteries was performed only in the DCVAS cohort at the discretion of the physician. FDG-PET imaging was available for some patients within the DCVAS cohort and for all patients in the NIH cohort. Clinical radiologists at each participating institution assessed the vascular imaging data focused upon 11 key territories: right and left carotid, subclavian, axillary, and renal arteries; mesenteric arteries; and descending and abdominal aorta. Angiographic and ultrasound lesions were defined as stenosis, occlusion, or aneurysm. Additionally, presence of abnormal arterial wall thickness on angiogram was incorporated into the definition of arteriographic lesions only in the CCF cohort. FDG-PET scans were assessed according to local practices or as previously reported (17, 18).

Statistical analysis:

Cluster analysis was used to identify groups of patients with similar patterns of arterial disease. Patients were clustered based on disease within the 11 key arterial territories. The optimal number of clusters was determined prior to clustering (NbClust) using the “silhouette” and “gap” indices and empirically testing a range of alternative cluster solutions (19). K-means clustering, an unsupervised machine learning algorithm, was then performed (Factoextra) (20). Cluster assignment was determined based on minimizing the Euclidean distance between items and resulting centroid. The DCVAS and NA cohorts were used as the development and validation sets, respectively, and were independently clustered and compared.

A weighted proportion was calculated when comparing the percent of TAK and GCA within clusters to account for unequal proportions of TAK and GCA in the overall cohorts.

Weighted proportion was calculated as shown:

$$\text{weighted proportion of TAK in Cluster X} = \frac{\frac{\# \text{ TAK in Cluster X}}{\# \text{ TAK in Cohort}}}{\left(\frac{\# \text{ TAK in Cluster X}}{\# \text{ TAK in Cohort}}\right) + \left(\frac{\# \text{ GCA in Cluster X}}{\# \text{ GCA in Cohort}}\right)}$$

Since the type of imaging modality used to assess the vasculature could influence the observed patterns of disease, a sensitivity analysis was performed by studying previously derived cluster assignment only in patients who had comprehensive imaging assessment of the large arteries. Comprehensive assessment was defined as having either angiography or ultrasonography to assess vascular damage (i.e. stenosis, occlusion, or aneurysm) and FDG-PET to assess vascular inflammation (i.e. arterial FDG-uptake). This analysis included every patient from the NIH cohort who underwent whole body angiography and FDG-PET per a vascular imaging protocol and a subset of patients from DCVAS who underwent angiography/ultrasonography and FDG-PET at the discretion of the physician. To determine whether disease within a cluster was primarily defined by vascular damage or inflammation, the percentage of arterial involvement defined by angiography/ultrasonography versus FDG-PET was calculated for the key arterial territories that defined each cluster.

Chi-square tests were used, and a p value <0.05 defined statistical significance. All analyses were performed using RStudio 1.1.3 and JMP V14.1 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Subject characteristics

A total of 1,068 patients were included in this study. The DCVAS cohort included 678 patients with large-vessel involvement from 62 study sites representing 26 countries and five continents, including 461 patients with TAK and 217 patients with GCA. The combined NA cohorts included 390 patients with large-vessel involvement, 225 patients with TAK and 165 patients with GCA. Baseline demographics are provided in Supplementary Table 1.

Frequency of arterial territory involvement

The frequency of involvement in individual arterial territories was compared by disease (Supplementary Table 2). In the DCVAS cohort, patients with TAK compared to patients with GCA were significantly more likely to have involvement of the left carotid (46.4% vs 29.5%, $p<0.001$), left subclavian (56.2% vs 37.2%, $p<0.001$), mesenteric (28.9% vs 1.4%, $p<0.001$), and renal arteries (left: 23.4% vs 1.4%, $p<0.001$; right: 22.1% vs 1.4%, $p<0.001$). In the DCVAS cohort, patients with GCA compared to patients with TAK were significantly more likely to have involvement of the descending thoracic aorta (41.0% vs 22.3%, $p<0.001$) and axillary arteries (left: 30.9% vs 5.9%, $p<0.001$; right: 31.8% vs 5.4%, $p<0.001$). In the NA cohort, patients with TAK compared to patients with GCA were significantly more likely to have involvement of the abdominal aorta (39.6% vs 28.5%, $p<0.001$), left carotid (52.9% vs 29.7%, $p<0.001$), mesenteric (37.8% vs 21.8%, $p<0.001$), and renal arteries (left: 26.2% vs 10.9%, $p<0.001$; right: 25.3% vs 15.8%, $p=0.024$). In the NA cohort, patients with GCA compared to patients with TAK were significantly more likely to have involvement of the axillary arteries (left: 42.4% vs 15.1%, $p<0.001$; right: 29.7% vs 12.4%, $p<0.001$).

The frequency of involvement in individual arterial territories was also compared across cohorts. When there were differences by cohort, more arterial involvement was consistently detected in the NA cohorts. When compared to the DCVAS cohort, patients with TAK in the NA cohort were more likely to have involvement of the descending thoracic aorta (40.4% vs 22.3%, $p<0.001$). When compared to the DCVAS cohort, patients with GCA in the NA cohort were more likely to have involvement of the subclavian (left: 61.8% vs 37.2%, $p<0.0001$; right: 53.9% vs 34.6%, $p<0.001$), mesenteric (21.8% vs 1.4%, $p<0.001$), and renal (left: 10.9% vs 1.4%, $p<0.001$; right: 15.8% vs 1.4%, $p<0.001$) arteries.

Differences in type of imaging modality used to assess disease

Frequency of the imaging modality used to assess arterial disease within the DCVAS and NA cohorts is displayed in Supplementary Table 3. Compared to patients with GCA, patients with TAK were more likely to have angiography (95.2% vs 50.2%, $p<0.001$) and less likely to have ultrasonography (28.4% vs 51.6%, $p<0.001$) or FDG-PET imaging (13.7% vs 57.6%, $p<0.001$). All patients in the NA cohort had angiography but only patients from the NIH had FDG-PET imaging, representing 22.1% of the combined NA cohort.

Identification of disease subgroups

In the DCVAS cohort, cluster analysis revealed six unique clusters of patients (Figure 1). Distinct patterns of arterial involvement were observed when comparing arterial frequency among clusters (Table 1). Patients with TAK were more likely than patients with GCA to be classified into Cluster One (19.5% vs 0.9%, $p<0.001$), Two (28.1% vs 9.2%, $p<0.001$), or Three (26.0% vs 11.1%, $p<0.001$) (Figure 2A) (Supplementary Table 4). The weighted proportion of TAK was higher than GCA within these clusters (Cluster One: 95.6% TAK vs 4.4% GCA; Cluster Two: 75.3% TAK vs 24.7% GCA; Cluster Three: 70.1% TAK vs 29.9% GCA) (Figure 1). Patients in Cluster One were likely to have involvement of the abdominal aorta, renal, and mesenteric arteries. Patients in Cluster Two were likely to have bilateral involvement of the carotid and subclavian arteries. Patients in Cluster Three were likely to have isolated involvement of the left subclavian artery with minimal involvement of the other arteries (Figure 3).

Patients with GCA were significantly more likely to be classified into Cluster Four (36.9% vs 18.7%, $p<0.001$), Five (21.2% vs 4.1%, $p<0.001$), or Six (20.7% vs 3.5%, $p<0.001$) compared to patients with TAK (Figure 2A, Supplementary Table 4). The weighted proportion of GCA was also higher than TAK within Clusters Four (66.4% GCA vs 33.6% TAK), Five (83.8% GCA vs 16.2% TAK), and Six (85.5% GCA vs 14.5% TAK) (Figure 1). Patients in Cluster Four had a low burden of disease in the large arteries not defined by a specific pattern of arterial involvement. Patients in Cluster Five had diffuse disease with involvement throughout the aorta and the aortic arch branch vessels. Patients in Cluster Six were more likely to have bilateral axillary and subclavian disease (Figure 4).

Validation of disease subgroups

The same six patterns of arterial involvement were validated in an independent analysis of the NA cohort; however, minor differences were seen in the prevalence of TAK and GCA patients between the clusters (Figure 2B, Supplementary Table 5). Patients with TAK remained significantly more likely to be classified into Cluster One (19.6% vs 5.5%, $p<0.001$), Two (26.2% vs 11.5%, $p=0.003$), or Three (26.7% vs 13.3%, $p=0.002$) (Figure 2B, Supplementary Table 4). Patients with GCA remained more likely than patients with TAK to be classified into Cluster Four (29.7% vs 16.9%, $p=0.003$) or Six (28.5% vs 3.1%, $p<0.0001$). Unlike the DCVAS cohort, in the NA cohort there was no significant difference in the prevalence of patients with TAK versus GCA in Cluster Five (7.6% vs 11.5%, $p=0.22$).

Influence of imaging modality on cluster assignment in DCVAS cohort

Since patients in the DCVAS cohort did not receive standardized imaging assessment, the association between type of imaging modality and cluster assignment was assessed. The majority of patients assigned to Clusters One, Two, Three, Four, or Six had angiography or ultrasonography (95.9%) and only 21.2% of these patients underwent FDG-PET (Supplementary Table 6). In Cluster Five, 69.2% of patients had either angiography or ultrasonography, and 87.7% had FDG-PET imaging.

Patients with TAK and GCA in Clusters One, Two, Three, Four, and Six were more likely to have stenotic, occlusive, or aneurysmal lesions by angiography/ultrasonography than vascular inflammation by FDG-PET. In Cluster Five, patients with TAK were more likely to have vascular damage detected by angiography or ultrasonography, and patients with GCA were more likely to have vascular inflammation detected by FDG-PET. Detailed distribution of arterial lesions by modality is displayed for each cluster by disease in Supplementary Tables 7–9.

Analysis Restricted to Patients with Comprehensive Imaging Assessment

In the DCVAS cohort, 143 patients (TAK=60; GCA=83) had both angiography or ultrasonography to assess vascular damage and FDG-PET to assess vascular inflammation. In the NIH cohort, 86 patients (TAK=47; GCA=39) had complete imaging. All six cluster patterns of arterial disease were again observed among patients with comprehensive imaging assessment (Figure 2C, Supplementary Table 4). Overall, patients with TAK were significantly more likely to have arterial damage without concomitant inflammation (52% vs 7%, $p<0.001$), and patients with GCA were significantly more likely to have vascular inflammation without concomitant damage (80% vs 23%, $p<0.001$) (Table 2). Concomitant damage and inflammation within an artery occurred more often in TAK than GCA (25% vs 13%, $p<0.001$). Among patients with comprehensive imaging, Clusters One, Two, and Three remained specific for TAK and were defined by vascular damage. Cluster Six remained specific for GCA and was defined by both vascular damage and inflammation. Cluster Five was specific for GCA and was defined primarily by vascular inflammation. Restriction of analysis to patients with comprehensive imaging assessment led to the inclusion of more patients with TAK into Cluster Five compared to the DCVAS cohort. However, patients with TAK in Cluster Five were more likely to have inflammation throughout the aorta (66%) and damage in the branch arteries (41%) whereas patients with GCA had inflammation in both the aorta (89%) and the branch arteries (85%) with little to no damage in the aorta (0%) or branch vessels (4%).

DISCUSSION

This study identified and validated six patterns of arterial disease in patients with LVV in large, independent, international cohorts. Three patterns were more specific for TAK, and three patterns were more specific for GCA; however, similarities between TAK and GCA were also observed. Arterial involvement was defined using both traditional (angiography and ultrasonography) and more advanced (FDG-PET) imaging techniques. Beyond differences in global patterns of disease, patients with TAK were more likely to have vascular damage and patients with GCA were more likely to have vascular inflammation without concomitant damage.

The majority of patients with TAK were grouped into three clusters. These patterns were consistent with angiographic patterns of disease previously reported by this study group (21). Patients with TAK were likely to have disease of the abdominal vasculature, bilateral disease of the subclavian and carotid arteries, or focal disease limited to the left subclavian artery. These patterns of disease were primarily driven by damage detected on angiography,

but the majority of patients with TAK in this study did not receive FDG-PET imaging. However, when analyses were restricted to patients with comprehensive imaging assessment, the same TAK-specific clusters were observed and remained heavily driven by damage rather than vascular inflammation.

The majority of patients with GCA were grouped into three clusters. Compared to TAK, patients with GCA were more likely to have bilateral damage in the subclavian and axillary arteries. In the DCVAS cohort, the majority of axillary disease was detected by ultrasonography and only 39% of these patients had corresponding bilateral subclavian disease. In the NA cohort, where patients received complete angiography, 91% of patients with bilateral axillary damage had corresponding bilateral subclavian damage. Lack of concomitant subclavian and axillary disease in the DCVAS cohort was likely due to suboptimal detection of disease in the subclavian arteries by ultrasonography. Diffuse involvement of the aorta and the branch vessels was another pattern observed in the DCVAS and NA cohorts, however, diffuse involvement was only specific for GCA in the DCVAS cohort. Classification of patients with GCA into this subset was largely driven by vascular inflammation identified by FDG-PET rather than damage identified by angiography or ultrasonography. Fewer patients with GCA underwent FDG-PET imaging in NA compared to the DCVAS cohort. When analyses were restricted to patients with comprehensive imaging assessment, more patients with GCA compared to TAK had diffuse disease. Further, patients with GCA with diffuse disease had inflammation in the aorta and the branch vessels with minimal associated vascular damage. The subset of patients with TAK with diffuse disease had inflammation in the aorta with extensive areas of luminal damage in the branch vessels. Finally, minimal arterial involvement in only a few vascular territories without a definable specific pattern of disease was seen more frequently in GCA than TAK. To what extent this subgroup represents patients with a low burden of vasculitis in the large arteries versus potential misclassification of vasculopathic lesions (e.g. atherosclerosis) as vasculitis is unclear.

Updated classification criteria that incorporate specific patterns of arterial disease could be useful to differentiate patients with TAK and GCA. The 1990 ACR criteria, the most recent classification criteria in large-vessel vasculitis, distinguish between TAK and GCA based primarily on cranial symptoms and differences in age of onset (15, 16). Because large-vessel involvement is not incorporated into the 1990 ACR classification criteria for GCA, only 40% of patients with large-vessel GCA meet the threshold for disease classification (22). Angiographic involvement of the large arteries is heavily represented in the 1990 ACR classification criteria for TAK; however, the criteria are biased towards arterial involvement of the limbs and do not specifically incorporate other patterns of vascular involvement (e.g. renal or mesenteric disease). Findings from this study suggest that the location of arterial disease and the nature of disease involvement (e.g. vascular damage with or without inflammation) should be considered in future classification criteria for LVV.

This study has several strengths to highlight. This is a large study conducted in TAK and large-vessel GCA, with a total of 1,068 patients. The large sample size enabled the use of sophisticated analytical techniques to identify global patterns of arterial disease. The resultant data-driven patterns of arterial disease were discovered and validated in

independent cohorts of patients with TAK and patients with GCA from different regions of the world. There have been several angiographic-classification systems proposed in TAK which have used empiric methods to identify subgroups of patients. Lupi-Herrera and Numano are the most commonly used angiographic classification systems in TAK and also define patterns of disease relative to involvement above and below the diaphragm (23–25). However, these systems were created in small regional cohorts and do not distinguish between TAK and GCA. Previous studies have used unbiased approaches to compare arterial involvement between TAK and GCA, but these studies clustered by artery rather than by patient to identify the structured relationship of involvement of one artery to other arteries within a single patient (i.e. if the left carotid artery is affected then the right carotid artery is also likely to be affected) (9, 10). This study clustered by patient rather than by artery to identify the relationship of one patient to another based on pattern of arterial disease. Data from this study may be particularly informative for clinicians to recognize common sites and patterns of large-vessel involvement in GCA. For example, angiography and ultrasonography can be useful to detect bilateral axillary disease, a pattern specific to GCA. Additionally, FDG-PET can be useful to identify a subset of patients with GCA with diffuse arterial inflammation without associated damage.

This study also has potential limitations to consider. Type of imaging modality and specific imaging protocols were not standardized and likely influenced the prevalence of arterial disease in specific territories. However, this study incorporates data from state-of-the-art imaging modalities and reflects current clinical practice in different parts of the world. In the DCVAS cohort, patients with GCA were less likely to have angiography, and patients with TAK were less likely to have FDG-PET. In the NA cohort, ultrasonography data was not available. Despite baseline differences in vascular assessment strategies, resultant imaging patterns remained consistent across the cohorts. Additionally, analyses restricted to a subset of patients with comprehensive imaging assessment demonstrated the same six clusters, suggesting that complete imaging would not change the observed global patterns of arterial disease. Arterial involvement by FDG-PET in absence of corresponding angiographic evidence of vascular damage was significantly more prevalent in GCA than TAK. Although arterial FDG uptake on PET can indicate vascular inflammation, it is possible that other factors such as atherosclerosis in an aging population with increased non-specific vascular FDG uptake (26) contributed to this observed difference. Study design precluded the ability to assess whether imaging subsets are associated with differential clinical outcomes. This should be assessed in future prospective studies. Involvement of the cranial arteries is a key differentiating feature between GCA and TAK but was not assessed in this study.

The widespread adoption of vascular imaging into the clinical assessment of LVV has led to a more nuanced understanding of similarities and differences between TAK and GCA. While involvement of the aorta and branch vessels is a defining feature of TAK, large artery disease has become increasingly recognized as a common feature of GCA. Although arterial involvement tends to be symmetric in paired arteries in both TAK and GCA (9), this study used unsupervised computer-driven approaches to identify global patterns of arterial disease that define subsets within each condition. Moreover, the identification of specific patterns of arterial disease is in part dependent on the type of imaging modality used to assess the vasculature. This is particularly true for a subset of patients with GCA who have vascular

inflammation on PET without corresponding damage. Differences in vascular territory involvement, along with emerging genome-wide association studies reporting different genetic susceptibilities (27, 28) and randomized trials demonstrating differences in responses to treatment (29–33), suggest that it remains relevant to classify TAK and GCA as distinct conditions. Arterial patterns of disease should be incorporated into future classification criteria in both TAK and GCA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

1. Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum.* 2006;55(1):131–7. [PubMed: 16463425]
2. Ostberg G Morphological changes in the large arteries in polymyalgia arteritica. *Acta Med Scand Suppl.* 1972;533:135–59. [PubMed: 4508179]
3. Ostberg G An arteritis with special reference to polymyalgia arteritica. *Acta Pathol Microbiol Scand Suppl.* 1973;237:Suppl 237:1–59.
4. Prieto-Gonzalez S, Arguis P, Garcia-Martinez A, Espigol-Frigole G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis.* 2012;71(7):1170–6. [PubMed: 22267328]
5. Grayson PC. Lumpers and splitters: ongoing issues in the classification of large vessel vasculitis. *J Rheumatol.* 2015;42(2):149–51. [PubMed: 25641963]
6. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? *Medicine (Baltimore).* 2009;88(4):221–6. [PubMed: 19593227]
7. Koster MJ, Warrington KJ. Classification of large vessel vasculitis: Can we separate giant cell arteritis from Takayasu arteritis? *Presse Med.* 2017;46(7–8 Pt 2):e205–e13. [PubMed: 28774474]
8. Arnaud L, Haroche J, Toledano D, Cacoub P, Mathian A, Costedoat-Chalumeau N, et al. Cluster analysis of arterial involvement in Takayasu arteritis reveals symmetric extension of the lesions in paired arterial beds. *Arthritis Rheum.* 2011;63(4):1136–40. [PubMed: 21452331]
9. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. *Ann Rheum Dis.* 2012;71(8):1329–34. [PubMed: 22328740]
10. Soriano A, Pazzola G, Boiardi L, Casali M, Muratore F, Pipitone N, et al. Distribution patterns of 18F-fluorodeoxyglucose in large vessels of Takayasu's and giant cell arteritis using positron emission tomography. *Clin Exp Rheumatol.* 2018;36 Suppl 111(2):99–106. [PubMed: 29799393]

11. Furuta S, Cousins C, Chaudhry A, Jayne D. Clinical features and radiological findings in large vessel vasculitis: are Takayasu arteritis and giant cell arteritis 2 different diseases or a single entity? *J Rheumatol.* 2015;42(2):300–8. [PubMed: 25399386]
12. Kermani TA, Crowson CS, Muratore F, Schmidt J, Matteson EL, Warrington KJ. Extra-cranial giant cell arteritis and Takayasu arteritis: How similar are they? *Semin Arthritis Rheum.* 2015;44(6):724–8. [PubMed: 25712813]
13. Luqmani RA, Suppiah R, Grayson PC, Merkel PA, Watts R. Nomenclature and classification of vasculitis - update on the ACR/EULAR diagnosis and classification of vasculitis study (DCVAS). *Clin Exp Immunol.* 2011;164 Suppl 1:11–3. [PubMed: 21447123]
14. Craven A, Robson J, Ponte C, Grayson PC, Suppiah R, Judge A, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). *Clin Exp Nephrol.* 2013;17(5):619–21. [PubMed: 23996327]
15. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum.* 1990;33(8):1129–34. [PubMed: 1975175]
16. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* 1990;33(8):1122–8. [PubMed: 2202311]
17. Grayson PC, Alehashemi S, Bagheri AA, Civelek AC, Cupps TR, Kaplan MJ, et al. (18) F-Fluorodeoxyglucose-Positron Emission Tomography As an Imaging Biomarker in a Prospective, Longitudinal Cohort of Patients With Large Vessel Vasculitis. *Arthritis Rheumatol.* 2018;70(3):439–49. [PubMed: 29145713]
18. Quinn KA, Ahlman MA, Malayeri AA, Marko J, Civelek AC, Rosenblum JS, et al. Comparison of magnetic resonance angiography and (18)F-fluorodeoxyglucose positron emission tomography in large-vessel vasculitis. *Ann Rheum Dis.* 2018;77(8):1165–71. [PubMed: 29666047]
19. Malika Charrad NG, Veronique Boiteau, Azam Niknafs(2014). NbClust: An R Package for Determining the Relevant Number of Clusters in a Data Set. *Journal of Statistical Software*, 61(6), 1–36. URL <http://www.jstatsoft.org/v61/i06/>.
20. Kassambara A, Mundt, Fabian(2017). factoextra: Extract and Visualize the Results of Multivariate Data Analyses. URL <https://CRAN.R-project.org/package=factoextra>.
21. Goel R, Gribbons KB, Maksimowicz-McKinnon K, Hoffman GS, Kumar S, Joseph G, et al. Discovery and Validation of Novel Disease Subsets in 806 Patients with Takayasu's Arteritis across Four International Cohorts [abstract]. *Arthritis Rheumatol.* 2018; 70 (suppl 10).
22. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: a cohort study. *Rheumatology (Oxford).* 2015;54(3):463–70. [PubMed: 25193809]
23. Hata A, Noda M, Moriwaki R, Numano F. Angiographic findings of Takayasu arteritis: new classification. *Int J Cardiol.* 1996;54 Suppl:S155–63. [PubMed: 9119518]
24. Lupi-Herrera E, Sanchez-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE. Takayasu's arteritis. Clinical study of 107 cases. *Am Heart J.* 1977;93(1):94–103. [PubMed: 12655]
25. Lupi E, Sanchez G, Horwitz S, Gutierrez E. Pulmonary artery involvement in Takayasu's arteritis. *Chest.* 1975;67(1):69–74. [PubMed: 14812]
26. Tawakol A, Migrino RQ, Bashian GG, Bedri S, Vermeylen D, Cury RC, et al. In vivo 18F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *J Am Coll Cardiol.* 2006;48(9):1818–24. [PubMed: 17084256]
27. Carmona FD, Vaglio A, Mackie SL, Hernandez-Rodriguez J, Monach PA, Castaneda S, et al. A Genome-wide Association Study Identifies Risk Alleles in Plasminogen and P4HA2 Associated with Giant Cell Arteritis. *Am J Hum Genet.* 2017;100(1):64–74. [PubMed: 28041642]
28. Renauer PA, Saruhan-Direskeneli G, Coit P, Adler A, Aksu K, Keser G, et al. Identification of Susceptibility Loci in IL6, RPS9/LILRB3, and an Intergenic Locus on Chromosome 21q22 in Takayasu Arteritis in a Genome-Wide Association Study. *Arthritis Rheumatol.* 2015;67(5):1361–8. [PubMed: 25604533]

29. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. *Arthritis Rheumatol.* 2017;69(4):837–45. [PubMed: 28133925]
30. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Takayasu Arteritis. *Arthritis Rheumatol.* 2017;69(4):846–53. [PubMed: 28133931]
31. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med.* 2017;377(4):317–28. [PubMed: 28745999]
32. Nakaoka Y, Isobe M, Takei S, Tanaka Y, Ishii T, Yokota S, et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann Rheum Dis.* 2018;77(3):348–54. [PubMed: 29191819]
33. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet.* 2016;387(10031):1921–7. [PubMed: 26952547]

SIGNIFICANCE AND INNOVATIONS

- Specific patterns of vascular disease differentiate subsets of patients with TAK from patients with GCA
- Compared to GCA, patients with TAK have more abdominal disease, symmetric arch disease, and isolated left subclavian disease
- Patterns of large artery involvement in GCA include bilateral axillary disease and diffuse vascular inflammation without associated damage

Figure 1.

Prevalence of arterial involvement by cluster assignment in the DCVAS cohort

Heatmaps of the large arteries indicating the percent of patients in each cluster with involvement of the 11 arterial territories of interest (right and left carotid, subclavian, axillary, and renal arteries, mesenteric arteries, and descending and abdominal aorta). The darker the red indicates a greater percentage of patients in the cluster have involvement of the artery. The weighted proportion of patients with Takayasu's arteritis (TAK) and patients with giant cell arteritis (GCA) in each cluster are listed. Clusters One, Two, and Three were TAK specific in the DCVAS and North American (validation) cohort. Clusters Five and Six were GCA specific in the DCVAS cohort but only Cluster Six was GCA specific in the North American cohort.

Figure 2.

Takayasu's arteritis and giant cell arteritis prevalence between the clusters by cohort

The percent of Takayasu's arteritis (TAK) and giant cell arteritis (GCA) patients in each cluster in the (A) DCVAS, (B) North American, and (C) Restricted cohorts. Restricted cohort refers to patients from the DCVAS cohort and the NIH cohort with comprehensive imaging assessment, defined as angiography or ultrasonography and positron emission tomography.

Figure 3.

Representative images of Takayasu's arteritis (TAK) predominant clusters

(A) Representative angiography of a patient classified as Cluster One. Patient with TAK has stenoses of the abdominal aorta and bilateral renal arteries (red arrows). (B) Representative angiography of patient classified as Cluster Two. Patient with TAK has stenosis of the right subclavian artery and occluded bilateral carotid arteries (red arrows). Blue arrows indicate an aorto-carotid bypass graft. (C) Representative angiography of patient with TAK classified as Cluster Three. Patient has isolated stenosis of the left subclavian artery (red arrows).

A.

Cluster Five

B.

Cluster Six

Figure 4.

Representative images of giant cell arteritis (GCA) predominant clusters

(A) Representative FDG-PET scan of patient classified as Cluster Five. Patient with GCA had diffuse FDG uptake in the aorta, subclavian, axillary, and vertebral arteries (red arrows).

(B) Representative angiography of patient with GCA classified as Cluster Six. Patient has bilateral stenosis of the axillary and subclavian arteries (red arrows).

Table 1.

Frequency of arterial involvement by cluster in the DCVAS cohort

	Cluster 1 n=92	Cluster 2 n=150	Cluster 3 n=144	Cluster 4 n=166	Cluster 5 n=65	Cluster 6 n=61
% Takayasu's arteritis	90 (95.6)	130 (75.3)	120 (70.1)	86 (33.6)	19 (16.2)	16 (14.5)
% Giant cell arteritis	2 (4.4)	20 (24.7)	24 (29.9)	80 (66.4)	46 (83.8)	45 (85.5)
Descending Aorta	26 (28.3)	21 (14.0)	21 (14.6)	49 (29.5)	65 (100)	10 (16.4)
Abdominal Aorta	54 (58.7)	14 (9.3)	15 (10.4)	58 (34.9)	48 (73.8)	5 (8.2)
Left Axillary	0 (0.0)	8 (5.3)	7 (4.9)	3 (1.8)	19 (29.2)	57 (93.4)
Right Axillary	3 (3.3)	3 (2.0)	4 (2.8)	5 (3.0)	20 (30.8)	59 (96.7)
Left Carotid	36 (39.1)	130 (86.7)	30 (20.8)	20 (12.0)	48 (73.8)	14 (23.0)
Right Carotid	19 (20.7)	147 (98.0)	2 (1.4)	7 (4.2)	45 (69.2)	21 (34.4)
Mesenteric	60 (65.2)	23 (15.3)	24 (16.7)	21 (12.7)	5 (7.7)	3 (4.9)
Left Renal	90 (97.8)	6 (4.0)	9 (6.3)	3 (1.8)	1 (1.5)	2 (3.3)
Right Renal	77 (83.7)	5 (3.3)	13 (9.0)	7 (4.2)	0 (0.0)	3 (4.9)
Left Subclavian	44 (47.8)	74 (49.3)	144 (100.0)	1 (0.6)	53 (81.5)	24 (39.3)
Right Subclavian	31 (33.7)	79 (52.7)	53 (36.8)	15 (9.0)	50 (76.9)	28 (45.9)

Percentage of arterial involvement. The darker the red indicates that a greater percent of patients within that cluster have involvement of the artery. Percent of Takayasu's arteritis and giant cell arteritis refers to the weighted proportion of Takayasu's arteritis and giant cell arteritis in each cluster.

Table 2.

Frequency of damage and FDG-PET in key arterial territories of each cluster by disease in patients with comprehensive imaging assessment

	Damage Alone	FDG Alone	Both Damage and FDG
Takayasu's arteritis (n=107)	52%	23%	25%
Cluster One (n=11)	95%	0%	5%
Cluster Two (n=36)	53%	22%	25%
Cluster Three (n=21)	57%	19%	24%
Cluster Five (n=19)	33%	38%	29%
<i>Aorta</i>	17%	66%	17%
<i>Branch vessels</i>	41%	25%	34%
Cluster Six (n=2)	43%	0%	57%
Giant cell arteritis (n=122)	7%	80%	13%
Cluster One (n=1)	0%	100%	0%
Cluster Two (n=14)	4%	91%	5%
Cluster Three (n=14)	21%	50%	29%
Cluster Five (n=37)	3%	86%	11%
<i>Aorta</i>	0%	89%	11%
<i>Branch vessels</i>	4%	85%	11%
Cluster Six (n=14)	30%	46%	24%

Percentage refers to the proportion of key arterial territories with damage alone (stenosis, occlusion, aneurysm); 18F-fluorodeoxyglucose (FDG)-uptake alone; or both damage and FDG-uptake out of all key territories involved within each cluster. The key territories are as listed: Cluster One – left and right renal, and mesenteric arteries, and abdominal aorta; Cluster Two – left and right carotid and subclavian arteries; Cluster Three – left subclavian artery; Cluster Five – descending and abdominal aorta and left and right subclavian and carotid arteries; Cluster Six – left and right axillary and subclavian arteries. Patients in Cluster Four are not displayed because no key territories were specific for patients in this cluster. Subanalyses for Cluster Five are included, the key territories are as listed: Aorta – descending and abdominal aorta; Branch vessels – left and right subclavian and carotid arteries.