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New Features of Disease after Diagnosis in Six Forms of Systemic Vasculitis

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Abstract

Objective—To quantify the occurrence of features of vasculitis that initially present after diagnosis in 6 types of primary vasculitis.

Methods—Standardized collection of data on 95 disease manifestations in 6 vasculitides, including granulomatosis with polyangiitis (Wegener's, GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA), polyarteritis nodosa (PAN), giant cell arteritis (GCA), and Takayasu's arteritis (TAK), was performed within a set of multicenter longitudinal, observational cohorts. For each form of vasculitis, the frequency of disease-specific manifestations at diagnosis was compared to the cumulative frequency of each manifestation. The percentage of patients who initially developed “severe” manifestations after diagnosis, defined as organ- or life-threatening in the small and medium vessel vasculitides (GPA,

MPA, EGPA, PAN) and as ischemic/vascular in the large vessel vasculitides (GCA, TAK), was reported.

Results—Out of 838 patients with vasculitis, 490 (59%) experienced 1 new disease manifestation after diagnosis. On average, patients with vasculitis experienced 1.3 new manifestations after diagnosis (GPA - 1.9, MPA - 1.2, EGPA - 1.5, PAN - 1.2, GCA - 0.7, TAK - 1.0). New severe manifestations occurred after diagnosis in 224 (27%) out of 838 patients (GPA - 26%, MPA - 19%, EGPA - 21%, PAN - 23%, GCA - 24%, and TAK - 44%). Timing of onset of new manifestations was not significantly associated with disease duration.

Conclusion—A majority of patients with vasculitis develop new disease features after diagnosis, including a substantial number of new, severe manifestations. Ongoing assessment of patients with established vasculitis should remain broad in scope.

Keywords

vasculitis; granulomatosis with polyangiitis; microscopic polyangiitis; eosinophilic granulomatosis with polyangiitis; polyarteritis nodosa; Takayasu's arteritis; giant cell arteritis

INTRODUCTION

When caring for a patient with a chronic, relapsing disease, physicians often rely on the past medical history to guide ongoing clinical assessment with the assumption that features of relapse will likely resemble patterns of prior disease. The systemic vasculitides are diseases in which manifestations and patterns of disease onset are highly variable, relapse is common and unpredictable, and new features of disease can occur late into the course of illness.

The spectrum of disease involvement at diagnosis and later in the disease course has been reported for some, but not all, of the major idiopathic vasculitides. Prior studies focused mainly on the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides and typically reported the frequency of organ system involvement rather than providing information about specific manifestations¹⁻¹⁷. Understanding the frequency and type of new clinical manifestations of vasculitis that can occur following diagnosis will inform both clinical practice and assist in the development of classification and diagnostic criteria¹⁸. The objectives of this study were to quantify the occurrence of new features of vasculitis (organ system involvement and specific manifestations) after diagnosis in 6 types of vasculitis, including granulomatosis with polyangiitis (Wegener's, GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA/EGPA), polyarteritis nodosa (PAN), giant cell arteritis (GCA), and Takayasu's arteritis (TAK). By systematically profiling multiple forms of vasculitis, the frequency of manifestations can be compared across types of vasculitis and discussed with reference to existing literature.

MATERIALS AND METHODS

Patients enrolled in the Vasculitis Clinical Research Consortium (VCRC) longitudinal study cohorts from 2006-2012, representing 6 types of vasculitis, were selected for analysis. The VCRC is an NIH-supported, international, multi-center research infrastructure dedicated to conducting clinical research in different forms of vasculitis. All patients with GPA fulfilled

a modified version of the 1990 American College of Rheumatology (ACR) classification criteria¹⁹. All patients with MPA satisfied the Chapel Hill criteria for the disease²⁰. Since the existing 1990 ACR classification criteria for PAN²¹ do not well differentiate PAN from MPA¹⁸, an adapted version of these criteria was used to classify PAN. Patients were eligible to enroll into the PAN longitudinal cohort if they fulfilled one major criteria for disease (arteriographic abnormality, biopsy evidence of arterial wall inflammatory infiltrate, or neuropathy) and one minor criteria (weight loss > 4kg, skin findings, testicular pain, myalgias, diastolic blood pressure > 90mm Hg, abnormal kidney function, or ischemic abdominal pain) or if they fulfilled two major criteria. Patients with hepatitis B-related PAN or with cutaneous-only PAN were excluded from analysis. All patients with EGPA, GCA, or TAK fulfilled the respective 1990 ACR classification criteria for these diseases²²⁻²⁴.

Clinicians with expertise in vasculitis, representing 8 North American VCRC centers, performed quarterly comprehensive clinical assessments of patients enrolled in the VCRC longitudinal cohorts. Features of disease directly attributable to vasculitis were recorded at baseline and at successive study visits using standardized data collection forms. The incidence of each potential disease feature was assessed “at diagnosis” and “ever” (baseline visit) and “since last visit” (successive study visits). Demographic information was collected on each subject including age, sex, race, disease duration, length of study enrollment, and study site location. For the purpose of calculating disease duration, disease onset was defined as the date of initial diagnosis rather than the date of symptom onset or necessarily of treatment initiation.

The frequency of organ system involvement at diagnosis and at cumulative follow-up was described for each type of vasculitis and compared to similar published data from other vasculitis cohorts. The frequency of disease-specific manifestations at diagnosis was compared to the cumulative frequency of each manifestation, and the percentage of patients who developed one or more new disease manifestations after diagnosis was reported. A new disease manifestation was defined as a feature of disease first present after diagnosis. “Severe” manifestations were defined as those that were organ- or life-threatening in the small and medium vessel vasculitides (GPA, MPA, EGPA, PAN) and as ischemic/vascular in the large vessel vasculitides (GCA, TAK). For the vasculitides with granulomatous features (GPA, EGPA), a panel of vasculitis experts within the VCRC classified disease manifestations by consensus as either “granulomatous”, “vasculitic”, or “other,” and the percentage of patients who developed each type of manifestation after diagnosis was described. Manifestations were not defined at the subject level; rather, each potential disease manifestation was classified *a priori* as either severe or non-severe and as either granulomatous or vasculitic or other.

A list of the 95 manifestations assessed in this study divided into 15 organ-based categories, along with the classification of each type of manifestation (severe or non-severe; granulomatous, vasculitic, or other) is listed in the Appendix.

Data regarding thrombotic manifestations were recorded in the small and medium vessel vasculitides. Since it is unclear whether thrombosis is a disease manifestation of vasculitis or

an associated condition,²⁵ occurrence of thrombotic events at diagnosis and later in the disease course were analyzed and reported separately within this study.

To determine if the development of new manifestations was related to disease duration, separate analyses were performed in a subset of patients enrolled into the VCRC within one year of diagnosis. Among patients who experienced at least one episode of recurrent disease activity, as determined by the treating physician, logistic regression using generalized estimated equations to account for repeated measurements was used to determine if the odds of developing a new manifestation versus purely recurrent features of disease was related to disease duration. Additionally, the median time from diagnosis to initial flare in disease activity was compared between those patients who experienced a new manifestation versus those who only experienced recurrence of prior manifestations using Wilcoxon rank sum test. A flare in disease activity was determined based on the clinical judgment of the treating physician, and all treating physicians were experts in the clinical care of patients with vasculitis.

RESULTS

Data from 838 patients with vasculitis were available for analysis. Patient demographics are provided in **Table 1**. The number of patients and median disease duration for the vasculitides was: GPA 341, 6.0 years; MPA 26, 3.5 years; EGPA 117, 3.9 years; PAN 55, 3.7 years; GCA 178, 2.1 years; TAK 121, 5.6 years. The median time enrolled within the VCRC cohorts was 1.8 years (range 0-4.9 years).

Four-hundred ninety of 838 patients (59%) experienced at least 1 new disease manifestation after diagnosis (**Figure**). Depending on the type of vasculitis, at least 1 new disease manifestation occurred in 43%-69% of patients. On average, patients with vasculitis experienced 1.3 new manifestations after diagnosis (GPA - 1.9, MPA - 1.2, EGPA - 1.5, PAN - 1.2, GCA - 0.7, TAK - 1.0). A subset of patients with each type of vasculitis (7-28%) experienced 3 new manifestations after diagnosis. The 3 most frequent new manifestations for each type of vasculitis are listed in **Table 1**.

New severe manifestations occurred after diagnosis in 224 (27%) of 838 patients (GPA - 26%, MPA - 19%, EGPA - 21%, PAN - 23%, GCA - 26%, and TAK - 45%). Non-severe manifestations occurred after diagnosis in 311 (37%) of 838 patients (GPA - 52%, MPA - 15%, EGPA - 49%, PAN - 37%, GCA - 22%, and TAK - 13%). An equal proportion of patients with GPA or EGPA developed new “granulomatous” manifestations (GPA - 35%; EGPA - 32%) compared to new “vasculitic” manifestations (GPA -31%; EGPA -30%).

The frequency of organ system involvement for each type of vasculitis at diagnosis and at cumulative follow-up is listed and compared to published literature from other vasculitis cohorts in **Table 2**. Limited data was available from published reports on organ system involvement in the large vessel vasculitides as most of these studies preferentially reported the frequency of individual manifestations rather than organ system involvement. New involvement of the musculoskeletal system after diagnosis was common across all types of vasculitis (range 8-12%). Among the 484 patients with small vessel vasculitis (GPA, MPA,

EGPA), new ocular involvement (range 10-12%) and cutaneous involvement (range 9-18%) were frequently observed after diagnosis. Among the 299 patients with large vessel vasculitis, new nervous system involvement (GCA-9%, TAK-14%) frequently occurred after diagnosis.

Thrombotic disease was observed in a substantial number of patients with small and medium vessel vasculitis. Thrombotic disease at diagnosis was noted in GPA (5%), MPA (0%), EGPA (3%), and PAN (14%). New thrombotic disease, mostly venous thromboembolic events, first occurred after diagnosis in GPA (9%), MPA (12%), EGPA (6%), and PAN (13%).

The frequency of selected, severe disease manifestations at diagnosis and at cumulative follow-up, and the percentage of patients in whom the manifestation initially occurred after diagnosis for each type of vasculitis, is provided in **Table 3**. There was a striking spectrum of severe manifestations which first occurred after diagnosis, including alveolar hemorrhage (4%), claudication (11%), glomerular disease (7%), deafness (2%), and vision loss (2%).

A subset of 388 patients were enrolled into the VCRC longitudinal study cohorts within one year of diagnosis and followed for a median of 1.9 years (range 0-6.6 years). At least one active disease visit after diagnosis was documented in 131 of 388 (34%) patients and 53 patients had >1 active disease visits. New manifestations were noted in 115 (49%) of active visits. The odds of developing a new disease manifestation compared to recurrence of prior manifestations decreased by 11% for every 1 year increase in disease duration following diagnosis but the results were not statistically significant (odds ratio=0.89, 95% confidence interval 0.5-1.1, $p=0.2$). The median time from diagnosis to initial flare in disease activity did not significantly differ among those who experienced a new manifestation versus a recurrence of prior disease features (0.87 versus 0.93 years, $p=0.8$).

DISCUSSION

This study is the first of its kind to systematically evaluate clinical features of vasculitis across several forms of small, medium, and large vessel vasculitis. Based on comprehensive clinical assessment within the VCRC longitudinal observational cohorts, the frequency of new manifestations of vasculitis occurring after diagnosis was described in six different types of vasculitis. New features of disease after diagnosis were frequently observed across all types of vasculitis under study. Fifty-nine percent of patients with vasculitis developed new features of disease after diagnosis, and 27% of patients first developed life-threatening, organ-threatening, or ischemic features of disease later into the disease course. Adding to the complexity of clinical assessment of patients with established vasculitis, the likelihood of developing a new disease manifestation versus purely a recurrence of prior disease features was not significantly associated with the timing of disease flare in relationship to disease duration.

There were some surprising findings in the present study. In the GCA group, 14% of patients experienced vision loss at time of diagnosis which is consistent with the 14-20% incidence of vision loss in the modern era of glucocorticoid therapy.²⁶ Among patients with

no evidence of vision loss at diagnosis, 5 of 178 (3%) patients with GCA developed vision loss later in the disease course. Although new vision loss after diagnosis of GCA is uncommon, it can occur despite therapeutic intervention.^{27,28} Additionally, the most frequent new manifestation after diagnosis in GCA was polymyalgia rheumatica (PMR). Epidemiologic studies indicate that 16-20% of patients with PMR develop GCA, highlighting the prodromal aspect of PMR in relationship to GCA.²⁹⁻³¹ However, symptoms of PMR have been observed in 40-60% of patients with GCA and can occur at any time point during the disease course.³⁰ In one clinical trial, 16% of patients with GCA developed PMR later in the disease course²⁸, and clinical experience suggests that symptoms of PMR can be “unmasked” later in the disease course during tapering of glucocorticoids.

The number of patients with MPA in this study was fairly small, and the findings in MPA should therefore be interpreted with caution. However, the frequency and severity of new manifestations after diagnosis of MPA was similar to other forms of vasculitis. In this study, 3 of 25 (12%) patients with MPA developed new ocular symptoms after diagnosis (all 3 developed conjunctivitis/episcleritis) and an additional 3 patients developed new ENT symptoms (sinusitis-2, nasal crusts-1). It is possible that some patients diagnosed initially as MPA evolved into a GPA phenotype.

Overall, the frequency of disease involvement at diagnosis and later in the disease course was consistent with reported literature, when this data was available. Notably, there is considerable variability in the literature regarding the prevalence of cardiac involvement in GPA, with prior reports of prevalence of cardiac disease in GPA ranging from 4-25%, depending on the extent of screening and inclusion of patients without overt clinical cardiac disease. Increased morbidity from ischemic heart disease has been observed in GPA,⁴¹ but it is unclear whether coronary atherosclerosis is an associated condition or a direct manifestation of disease. In this study, coronary arteritis was not observed in any patients with GPA at any point in the disease course.

Thrombotic events were assessed and observed in a substantial number of patients with small and medium vessel vasculitis. Ample evidence supports an increased incidence of thromboembolic disease in ANCA-associated vasculitis, but there is minimal literature regarding thrombotic disease in PAN.²⁵ Surprisingly, the highest prevalence of thrombotic disease in this study was observed in PAN (27%) rather than AAV, and new thrombotic disease after diagnosis was the most frequent new manifestation later in the course of PAN.

This study has several notable strengths including relatively large study cohorts for these rare diseases, a comprehensive and standardized system to collect data on disease manifestations, and inclusion of multiple centers with expertise in the evaluation of patients with vasculitis.

This study also has some limitations to consider. It is possible that retrospective assessment of disease features at diagnosis, as performed for some patients in the cohorts, was biased towards preferential reporting of only the more severe manifestations. However, severe disease manifestations, such as glomerulonephritis, which are less susceptible to recall bias, were also frequently first observed after diagnosis. Referral bias may have influenced the

data if patients with more complicated disease courses may have been preferentially referred to tertiary care centers for ongoing management of vasculitis. However, recruitment of subjects from 8 centers may have helped reduce such bias. The influence of treatment on the development of new disease manifestations was not assessed; however, a significant number of new manifestations occurred in patients while they were under direct observation and presumably receiving standard of care therapy at tertiary care centers with expertise in vasculitis. As therapeutic advances continue to transform the systemic vasculitides from potentially fatal diseases if untreated into more chronic disorders, the findings in this report highlight that the majority of patients with vasculitis will experience new disease manifestations after initial diagnosis. Continued improvement in the management of patients with established vasculitis is needed.

A substantial number of variable disease features occur after diagnosis across many forms of vasculitis. These data could influence development of classification and diagnostic criteria since such criteria often focus on the initial presentation of disease. Similarly, these results provide insight important to physicians caring for patients with vasculitis. While previous patterns of disease may help guide clinical assessment of patients with relapsing systemic disease syndromes, ongoing clinical assessment of a patient with established systemic vasculitis should remain comprehensive and broad in scope.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med.* 1992; 116(6):488–98. [PubMed: 1739240]
2. Anderson G, Coles ET, Crane M, Douglas AC, Gibbs AR, Geddes DM, et al. Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. *Q J Med.* 1992; 83(302):427–38. [PubMed: 1448544]
3. Matteson EL, Gold KN, Bloch DA, Hunder GG. Long-term survival of patients with Wegener's granulomatosis from the American College of Rheumatology Wegener's Granulomatosis Classification Criteria Cohort. *Am J Med.* 1996; 101(2):129–34. [PubMed: 8757351]
4. Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum.* 2000; 43(5):1021–32. [PubMed: 10817555]
5. Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. *Arthritis Rheum.* 2003; 48(8):2299–309. [PubMed: 12905485]

6. Serra A, Cameron JS, Turner DR, Hartley B, Ogg CS, Neild GH, et al. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. *Q J Med.* 1984; 53(210):181–207. [PubMed: 6463195]
7. D'Agati V, Chander P, Nash M, Mancilla-Jimenez R. Idiopathic microscopic polyarteritis nodosa: ultrastructural observations on the renal vascular and glomerular lesions. *Am J Kidney Dis.* 1986; 7(1):95–110. [PubMed: 2867676]
8. Adu D, Howie AJ, Scott DG, Bacon PA, McGonigle RJ, Micheal J. Polyarteritis and the kidney. *Q J Med.* 1987; 62(239):221–37. [PubMed: 2889238]
9. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum.* 1999; 42(3):421–30. [PubMed: 10088763]
10. Agard C, Mouthon L, Mahr A, Guillevin L. Microscopic polyangiitis and polyarteritis nodosa: how and when do they start? *Arthritis Rheum.* 2003; 49(5):709–15. [PubMed: 14558058]
11. Chumbley LC, Harrison EG Jr, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. *Mayo Clin Proc.* 1977; 52(8):477–84. [PubMed: 18640]
12. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to the Churg-Strauss syndrome. *Medicine (Baltimore).* 1984; 63(2):65–81. [PubMed: 6366453]
13. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore).* 1999; 78(1):26–37. [PubMed: 9990352]
14. Keogh KA, Specks U. Churg-Strauss syndrome: clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. *Am J Med.* 2003; 115(4):284–90. [PubMed: 12967693]
15. Solans R, Bosch JA, Perez-Bocanegra C, Selva A, Huguet P, Alijotas J, et al. Churg-Strauss syndrome: outcome and long-term follow-up of 32 patients. *Rheumatology (Oxford).* 2001; 40(7):763–71. [PubMed: 11477281]
16. Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum.* 2005; 52(9):2926–35. [PubMed: 16142760]
17. Sable-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, et al. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med.* 2005; 143(9):632–8. [PubMed: 16263885]
18. Watts RA, Suppiah R, Merkel PA, Luqmani R. Systemic vasculitis--is it time to reclassify? *Rheumatology (Oxford).* 50(4):643–5. [PubMed: 20647295]
19. Design of the Wegener's Granulomatosis Etanercept Trial (WGET). *Control Clin Trials.* 2002; 23(4):450–68. [PubMed: 12161090]
20. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum.* 1994; 37(2):187–92. [PubMed: 8129773]
21. Lightfoot RW Jr, Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum.* 1990; 33(8):1088–93. [PubMed: 1975174]
22. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum.* 1990; 33(8):1094–100. [PubMed: 2202307]
23. 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]
24. 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]

25. Tomasson G, Monach PA, Merkel PA. Thromboembolic disease in vasculitis. *Curr Opin Rheumatol.* 2009; 21(1):41–6. [PubMed: 19077717]
26. Fraser JA, Weyand CM, Newman NJ, Biousse V. The treatment of giant cell arteritis. *Rev Neurol Dis.* 2008; 5(3):140–52. [PubMed: 18838954]
27. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum.* 2002; 46(5):1309–18. [PubMed: 12115238]
28. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med.* 2007; 146(9):621–30. [PubMed: 17470830]
29. Franzen P, Sutinen S, von Knorring J. Giant cell arteritis and polymyalgia rheumatica in a region of Finland: an epidemiologic, clinical and pathologic study, 1984–1988. *J Rheumatol.* 1992; 19(2): 273–6. [PubMed: 1629827]
30. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med.* 1995; 123(3):192–4. [PubMed: 7598301]
31. Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med.* 2002; 347(4):261–71. [PubMed: 12140303]
32. Fortin PR, Larson MG, Watters AK, Yeadon CA, Choquette D, Esdaile JM. Prognostic factors in systemic necrotizing vasculitis of the polyarteritis nodosa group--a review of 45 cases. *J Rheumatol.* 1995; 22(1):78–84. [PubMed: 7699687]
33. Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum.* 2010; 62(2):616–26. [PubMed: 20112401]
34. Guillevin L, Le Thi Huong D, Godeau P, Jais P, Wechsler B. Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. *Br J Rheumatol.* 1988; 27(4):258–64. [PubMed: 2900659]
35. Calamia KT, Hunder GG. Clinical Manifestations of Giant-Cell (Temporal) Arteritis. *Clinics in Rheumatic Diseases.* 1980; 6(2):389–403.
36. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum.* 1999; 42(2):311–7. [PubMed: 10025926]
37. Nakao K, Ikeda M, Kimata S, Niitani H, Niyahara M. Takayasu's arteritis. Clinical report of eighty-four cases and immunological studies of seven cases. *Circulation.* 1967; 35(6):1141–55. [PubMed: 5298313]
38. Koide K. Takayasu arteritis in Japan. *Heart Vessels Suppl.* 1992; 7:48–54. [PubMed: 1360971]
39. Jain S, Kumari S, Ganguly NK, Sharma BK. Current status of Takayasu arteritis in India. *Int J Cardiol.* 1996; 54(Suppl):S111–6. [PubMed: 9119512]
40. Kerr G. Takayasu's arteritis. *Curr Opin Rheumatol.* 1994; 6(1):32–8. [PubMed: 7913334]
41. Faurschou M, Mellekjaer L, Sorensen IJ, Svalgaard Thomsen B, Dreyer L, Baslund B. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. *Arthritis Rheum.* 2009; 60(4):1187–92. [PubMed: 19333952]

GPA: granulomatosis with polyangiitis (Wegener's); MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis (Churg-Strauss); PAN: polyarteritis nodosa; GCA: giant cell arteritis; TAK: Takayasu's arteritis.

Figure.

Frequency of New Disease Manifestations Occurring after Diagnosis in 6 Types of Vasculitis

Table 1
Study Characteristics and the 3 Most Frequently Observed New Manifestations after Diagnosis

Type of Vasculitis	Disease Duration (years, median, range)	Enrollment in VCRC Cohort (years, median, range)	Age at Enrollment (years, median, range)	Sex	Race	Most Frequent New Manifestation after Diagnosis (% subjects)
Granulomatosis with polyangiitis (n=341)	6.0 (0-30.5)	2.2 (0-4.7)	50.6 (12-87)	F: 181 (53%) M: 160 (47%)	C: 317 (93%) AA: 6 (2%) A: 10 (3%) O: 8 (2%)	Arthralgias (11%) Rhinitis (9%) Glomerular disease (9%)
Microscopic polyangiitis (n=26)	3.5 (0-10.8)	1.5 (0-4.2)	57.7 (19-82)	F: 19 (73%) M: 7 (27%)	C: 22 (84%) AA: 2 (8%) A: 1 (4%) O: 1 (4%)	Glomerular disease (11%) Arthralgias (8%) Alveolar Hemorrhage (8%)
Eosinophilic granulomatosis with polyangiitis (n=117)	3.9 (0-24.7)	1.9 (0-4.8)	52.2 (21-81)	F: 64 (55%) M: 53 (45%)	C: 108 (92%) AA: 2 (2%) A: 4 (4%) O: 3 (2%)	Nasal polyp (10%) Pulmonary infiltrate (9%) Purpura (8%)
Polyarteritis nodosa (n=55)	3.7 (0-21.0)	1.7 (0-4.8)	49.2 (18-79)	F: 25 (45%) M: 30 (55%)	C: 48 (87%) AA: 3 (6%) A: 2 (4%) O: 2 (3%)	Motor mononeuritis (12%) Arthralgias (12%) Sensory Neuropathy (8%)
Giant cell arteritis (n=178)	2.1 (0-17.8)	1.2 (0-4.3)	71.2 (54-91)	F: 141 (79%) M: 37 (21%)	C: 170 (95%) AA: 4 (2%) A: 3 (2%) O: 1 (1%)	Polymyalgia rheumatica (11%) Headache (7%) Arthralgias (7%)
Takayasu's arteritis (n=121)	5.6 (0-29.3)	1.6 (0-4.9)	39 (9-65)	F: 112 (93%) M: 9 (7%)	C: 104 (86%) AA: 7 (6%) A: 8 (7%) O: 2 (1%)	Arm claudication (14%) Lightheadedness (8%) Carotidynia (7%)

F: female; M: male; C: Caucasian; AA: African American; A: Asian; O: other.

Table 2
Organ System Involvement within the Vasculitis Clinical Research Consortium (VCRC) and Comparison to Existing Literature

Organ System	Assessment	GPA	MPA	EGPA	PAN	GCA	TAK						
		VCRC	Lit. 1-5	VCRC	Lit. 6-10	VCRC	Lit. 11-17	VCRC	Lit. 18-35	VCRC	Lit. 36-37	VCRC	Lit. 38-41
Constitutional	At diagnosis	79%	NI	88%	75%	85%	69%	67%	81-93%	38%	22%	32%	63-67%
	Cumulative	88%	NI	93%	73-79%	89%	68-81%	77%	NI	41%	NI	40%	43-67%
Musculoskeletal	At diagnosis	61%	20-66%	50%	56%	47%	38%	63%	44-47%	58%	NI	73%	NI
	Cumulative	73%	67-81%	62%	51-56%	57%	20-46%	71%	NI	69%	NI	82%	53%
Cutaneous	At diagnosis	27%	13-27%	31%	53%	44%	69%	50%	28-58%	1%	NI	5%	NI
	Cumulative	36%	33-46%	42%	25-62%	62%	51-81%	59%	44-58%	2%	NI	9%	NI
Mucous Membranes	At diagnosis	11%	11%	0%	NI	4%	NI	4%	NI	NA	NI	NA	NI
	Cumulative	16%	NI	4%	NI	5%	NI	6%	NI	NA	NI	NA	NI
Ocular	At diagnosis	26%	14-40%	0%	NI	4%	6%	6%	8%	30%	NI	7%	12-24%
	Cumulative	38%	52-61%	12%	28-30%	14%	7-16%	12%	NI	35%	NI	9%	NI
Ear, nose, throat	At diagnosis	86%	73-93%	19%	NI	78%	NI	NA	NI	NA	NI	NA	NI
	Cumulative	91%	92-99%	31%	20-30%	85%	47-77%	NA	NI	NA	NI	NA	NI
Cranial	At diagnosis	NA	NI	NA	NI	NA	NI	NA	NI	79%	NI	41%	NI
	Cumulative	NA	NI	NA	NI	NA	NI	NA	NI	83%	NI	50%	NI
Cardiac	At diagnosis	2%	2-13%	4%	17%	16%	28%	14%	17-20%	1%	NI	10%	55%
	Cumulative	5%	4-25%	15%	9-17%	21%	16-52%	15%	18-23%	3%	NI	17%	38-55%
Gastrointestinal	At diagnosis	1%	2-3%	4%	22%	13%	38%	42%	31-53%	1%	NI	4%	9%
	Cumulative	3%	6-19%	12%	31-56%	20%	17-62%	48%	31-53%	2%	NI	7%	NI
Genitourinary	At diagnosis	NA	NI	NA	NI	NA	NI	10%	3%	NA	NI	NA	NI
	Cumulative	NA	NI	NA	NI	NA	NI	12%	NI	NA	NI	NA	NI
Pulmonary	At diagnosis	64%	45-63%	65%	22%	97%	100%	NA	NI	NA	NI	NA	NI
	Cumulative	70%	53-85%	69%	25-55%	99%	96-100%	NA	NI	NA	NI	NA	NI
Kidney	At diagnosis	45%	18-60%	73%	19%	11%	13%	29%	22%	1%	NI	16%	NI
	Cumulative	54%	68-77%	81%	79-100%	17%	13-42%	38%	29-44%	1%	NI	19%	NI
Nervous system	At diagnosis	17%	9-21%	19%	72%	57%	44%	58%	74-92%	5%	NI	25%	65%
	Cumulative	24%	14-40%	26%	28-72%	67%	50-78%	63%	51-92%	14%	15%	39%	57-65%
Thrombotic disease	At diagnosis	5%	NI	0%	NI	3%	NI	14%	NI	NA	NI	NA	NI

Organ System	Assessment	GPA		MPA		EGPA		PAN		GCA		TAK	
		VCRC	Lit. ¹⁻⁵	VCRC	Lit. ⁶⁻¹⁰	VCRC	Lit. ¹¹⁻¹⁷	VCRC	Lit. ^{10,33-35}	VCRC	Lit. ^{36,37}	VCRC	Lit. ³⁸⁻⁴¹
Other features	Cumulative	14%	NI	12%	NI	9%	NI	27%	NI	NA	NI	NA	NI
	At diagnosis	4%	NI	0%	NI	8%	NI	12%	NI	13%	NI	27%	NI
	Cumulative	7%	NI	0%	NI	12%	NI	14%	NI	14%	NI	27%	NI

Lit: published literature from other vasculitis cohorts; NA: not assessed; NI: no information. GPA: granulomatosis with polyangiitis (Wegener's); MPA: microscopic polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis (Churg-Strauss); PAN: polyarteritis nodosa; GCA: giant cell arteritis; TAK: Takayasu's arteritis

Table 3

Frequency and Timing of Selected Disease Manifestations

Manifestation *	Total		% Patients In Whom Manifestation Initially Occurred After Diagnosis					
	At Diagnosis	Cumulative	GPA n=341	MPA n=26	EGPA n=117	PAN n=55	GCA n=178	TAK n=121
Alveolar hemorrhage	75/484 (15%)	93/484 (19%)	4%	8%	3%	NA	NA	NA
Claudication (arm or leg)	99/299 (33%)	131/299 (44%)	NA	NA	NA	NA	6%	17%
Coronary arteritis	3/539 (<1%)	4/539 (<1%)	0% [†]	0% [†]	1%	0%	NA	NA
Cranial nerve palsy	9/539 (2%)	17/539 (3%)	1%	0%	3%	2%	NA	NA
Dialysis	18/539 (3%)	25/539 (5%)	1%	8%	0% [†]	0%	NA	NA
Gangrene	8/539 (2%)	13/539 (2%)	1%	0% [†]	1%	2%	NA	NA
Glomerular disease [§]	172/539 (32%)	210/539 (39%)	9%	11%	3%	4%	NA	NA
Meningitis	3/484 (1%)	5/484 (1%)	1%	0%	0%	NA	NA	NA
Mesenteric ischemia	14/539 (3%)	19/539 (4%)	1%	4%	0%	4%	NA	NA
Motor mononeuritis	67/539 (12%)	83/539 (15%)	<1%	4%	5%	12%	NA	NA
Scleritis	20/484 (4%)	26/484 (5%)	2%	0% [†]	1%	NA	NA	NA
Sensorineural deafness	21/484 (4%)	30/484 (6%)	2%	0%	1%	NA	NA	NA
Sensory neuropathy	111/539 (21%)	141/539 (26%)	5%	0%	7%	8%	NA	NA
Stroke	11/838 (1%)	17/838 (2%)	0%	0% [†]	0%	2%	1%	4%
Vision loss (partial or severe)	42/299 (14%)	48/299 (16%)	NA	NA	NA	NA	3%	<1%

GPA: granulomatosis with polyangiitis (Wegener's); MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis (Churg-Strauss); PAN: polyarteritis nodosa; GCA: giant cell arteritis; TAK: Takayasu's arteritis; NA- not assessed in that type of vasculitis.

* Manifestation must be directly attributable to vasculitis.

[†] Indicates that the manifestation was never present in any patient with that form of vasculitis at any point during the disease course.

[§] Glomerular disease is defined as presence of either proteinuria, hematuria, or red blood cell casts.