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The clinical spectrum of Medium-sized Vessel Vasculitis

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ABSTRACT

Objectives: Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis of medium-sized visceral vessels. However, cutaneous arteritis (CA) and gastrointestinal (GI) vasculitis are forms of single organ vasculitis having indistinguishable histopathological findings from PAN. The aim of this study was to evaluate and compare the clinical characteristics, treatment, and outcomes of patients with systemic PAN, CA and GI vasculitis.

Methods: Retrospective cohorts were assembled of patients with PAN, CA and GI vasculitis between 1980 and 2014. The demographics, clinical characteristics, treatment and outcomes of patients were abstracted from medical records.

Results: We included 48 patients with PAN, 41 patients with CA, and 19 patients with GI vasculitis. One patient presenting as CA evolved to systemic PAN during the disease course. At diagnosis, 94% of patients with PAN, 93% of patients with CA and 67% of patients with GI vasculitis were treated with glucocorticoids. Additional immunosuppressive agents were used in 67% of PAN, 37% of GI vasculitis and 32% of CA. The five-year cumulative relapse rate was 45.2% in CA, and only 9.6% in PAN during follow-up of about 6 years.No deaths were observed in the CA group.Survival at 10-years was 66% in the PAN and 61% in GI vasculitis group.

Conclusion: Systemic PAN, CA and GI vasculitis demonstrate different clinical courses and therefore may be different diseases rather than a spectrum of the same disease. Progression of CA to systemic PAN is very rare. Relapse risk is low during follow-up in PAN. Patients with CA have a higher relapse rate compared to those with systemic PAN, possibly due to lower use of immunosuppressive therapy in the former group.

Significance and Innovations

- ✓ Systemic PAN, CA and GI vasculitis demonstrate different clinical courses and therefore may be different diseases rather than a spectrum of the same disease.
- ✓ Progression of CA to systemic PAN is very rare.
- ✓ Vasculitis related damage is comparable between systemic PAN and GI vasculitis.
- ✓ The risk of relapse is very low in patients with systemic PAN.
- ✓ Patients with CA have a higher relapse rate compared to those with systemic PAN, possibly due to lower use of immunosuppressive agents.

INTRODUCTION

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis predominantly affecting medium-sized visceral arteries and their branches, with an estimated annual incidence of 2-9/million adults.[1,2] Skin and peripheral nervous system manifestations are the most common clinical findings, while glomerulonephritis is typically absent.[3] Gastrointestinal manifestations are also frequently seen, and are among the most important predictors of mortality and morbidity.[4] A form of PAN limited to the skin, with no systemic involvement, was first defined as cutaneous PAN by Lindberg.[5] To date, the progression of cutaneous PAN to systemic PAN has been rarely reported.[6]

Vasculitic involvement of the gastrointestinal (GI) system is a well-known manifestation of small and medium-sized vessel vasculitides. It is common in PAN, ANCA-associated vasculitis and IgA vasculitis (Henoch Schönlein purpura).[7,8] The presence of GI manifestations in systemic vasculitis is associated with a worse prognosis.[9] Vasculitis limited to the GI system can rarely be observed as a form of single organ vasculitis (SOV), and is also associated with significant morbidity and mortality.[10] Histopathologic and angiographic findings of necrotizing vasculitis limited to the GI system cannot be distinguished from PAN.

The revised 2012 International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides includes additional categories of vasculitis such as SOV and vasculitis associated with probable etiology. SOV was defined as a vasculitis affecting any size artery and/or vein in a single organ with no systemic manifestations. Following the CHCC nomenclature, cutaneous PAN is now termed cutaneous arteritis (CA), a form of SOV. PAN is now divided according to etiology, with hepatitis B virus (HBV)-associated PAN considered separately from idiopathic systemic PAN.[1]

Even though the clinical characteristics and outcomes of these conditions have been reported separately, there are no studies that have directly compared PAN, CA and GI vasculitis. The aim of this study was to evaluate and compare the clinical characteristics, treatment, and outcomes of patients with systemic PAN, CA and GI vasculitis.

METHODS

Patient population

A retrospective cohort study, including 108 patients evaluated at Mayo Clinic, Rochester, Minnesota between January 1980 and December 2014 was performed. The longitudinal medical records of 1515 patients were reviewed by a rheumatologist (FAO), including all patients with the diagnostic code of polyarteritis nodosa (ICD-9 446.0) as well as all patients with the following key terms documented in their medical record: medium vessel vasculitis, mesenteric vasculitis, (localized) vasculitis of the gastrointestinal tract, gallbladder vasculitis, periarteritis nodosa, testicular vasculitis, cutaneous polyarteritis nodosa, cutaneous arteritis, limited polyarteritis nodosa, PAN, hepatitis-B associated vasculitis. Confirmed GI vasculitis cases previously reported by this group[10] and additional cases identified over the extended study period were included. Patients were classified according to the 1990 American College of Rheumatology (ACR) classification criteria for PAN[11] and the 2012 International CHCC nomenclature to identify the appropriate vasculitis categories. Patients diagnosed within 12 months of their first evaluation at Mayo Clinic and having data related to first diagnosis were included. Patients who had necrotizing vasculitis with proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA positivity were excluded. The study was approved by the institutional review board at Mayo Clinic.

Data collection

Data on demographics, clinical characteristics, laboratory and imaging findings, treatment and outcomes were abstracted from the medical record and documented in an electronic data capture program (REDCap).

Definitions

Vasculitis on angiography: Arteriogram showing segmental narrowing, dilatation, occlusion or aneurysms of visceral arteries in the absence of vessel changes of atherosclerosis or vasculitis mimics such as fibromuscular dysplasia) and confirmation by an expert radiologist that findings were consistent with vasculitis.

Polyarteritis nodosa: PAN was defined based on presence of at least 3 of 10 criteria according to ACR 1990 classification criteria for PAN.[11] Twenty-five of 48 patients with PAN also met the CHCC 2012 histopathologic definition of 'necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and not associated with ANCA'.[1]

Single-organ vasculitis: SOV was defined as vasculitis in arteries or veins of any size in a single organ,with no features to indicate it as a manifestation of systemic vasculitis according to CHCC 2012 definition.[1] Necrotizing vasculitis limited to the gastrointestinal system or evidence of typical angiographic findings in GI vessels was classified as GI vasculitis. Necrotizing medium vessel vasculitis limited to the skin was classified as CA. Patients with isolated small vessel vasculitis in skin biopsies were excluded.

Disease Assessment

Disease activity: Disease activity was assessed at all visits using the Birmingham Vasculitis Activity Score (BVAS) version 3 rating 56 items derived from evaluations in 9 systems or organ groups.[12] *Remission* was defined as absence of disease activity attributable to vasculitis for ≥ 3 months (BVAS=0). *Relapse* was defined as the reoccurrence of vasculitic manifestations (BVAS>0) which required addition of or a change in immunosuppressive agents, the restart of steroid treatment, and/or an increased steroid dose in a patient following a ≥3 month period of clinical remission.. *Failure* was defined as absence of clinical remission, occurrence of new vasculitis manifestation(s) or death before remission was obtained.[13]

Prognosis: The prognostic Five-Factor Score (FFS), which includes parameters predictive of poorer outcome and mortality (creatinine > 1.58mg/dl, proteinuria > 1g/24h, gastrointestinal involvement, cardiomyopathy, CNS involvement) was calculated at diagnosis.[14]

Damage assessment: The Vasculitis Damage Index (VDI), the only validated damage assessment measure for systemic vasculitis, was used to determine the extent of vasculitic-induced damage.[15] VDI score was calculated at the last visit for patients having follow-up.

Statistical analysis

Descriptive statistics (means, percentages, etc.) were used to summarize the data. Comparisons between patients with different types of vasculitic involvement (PAN, GI and CA) were performed using Chi-square and Wilcoxon rank-sum tests. Kaplan-Meier methods were used to estimate survival rates and the cumulative incidence of relapse in each group. Person-year methods were used to calculate relapse rates for each group allowing for multiple relapses per patient. Rate ratios with 95% confidence intervals were calculated assuming the occurrence of relapses followed the Poisson distribution. Risk factors for mortality and first relapse were examined using univariable Cox proportional hazards models. Statistical analyses were performed using SAS (Version 9.4; SAS Institute, Cary, NC) and R (Version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria) statistical packages.

RESULTS

Baseline characteristics

The study included 48 patients with PAN, 41 patients with CA, and 19 patients with GI vasculitis. One patient did not fulfill the ACR 1990 criteria but met the CHCC definition for PAN. This patient was included in the PAN group based on expert opinion (study authors). Only 1 patient presenting as CA evolved into systemic PAN during the disease course. While there was a male predominance in PAN group, there was female predominance in the CA and GI vasculitis groups. The demographic and laboratory characteristics of patients at diagnosis are presented in Table 1.

Most cases of PAN were idiopathic. Seven patients had hepatitis B surface antigen (HBsAg) positivity and 2 patients had hepatitis C antibody (Anti-HCV) positivity. Viral DNA was detected in 5 of 7 patients with hepatitis B positivity. Viral RNA was detected in both patients with hepatitis C positivity. Two patients with PAN had a history of long-term minocycline use which was implicated as a potential etiologic factor for the development of PAN. Among the GI vasculitis group, 1 patient had hepatitis C. Four of 7 PAN patients with hepatitis B positivity

were treated with antiviral agents together with immunosuppressive therapy. Two patients did not receive antiviral treatment due to absence of viremia. There were missing data regarding hepatitis B treatment for 1 patient. Two patients with PAN and 1 patient with GI vasculitis having hepatitis C positivity were not treated with antiviral agents during the course of this study.

At disease onset, constitutional (n=34, 71%), musculoskeletal (n=33, 69%), neurologic (n=27, 56%) and cutaneous manifestations (n=27, 56%) were the most common clinical features in the PAN group. Constitutional and musculoskeletal symptoms were less frequent in the CA and GI vasculitis groups. There was only 1 patient at baseline with neurologic symptoms in the CA group which manifested as a non-vasculitic, sensory, peripheral neuropathy due to focal nerve compression. The most common clinical feature in the CA group was subcutaneous nodules (61%), while ischemic abdominal pain was the predominant manifestation among the GI vasculitis group (89%). The clinical manifestations of all study patients are presented in Table 2.

A total of 43 tissue biopsy/resection samples were available for 35 patients in the PAN group: 21 skin, 7 surgically resected bowel, 5 nerve, 3 renal, 2 temporal artery, 2 testicular, 1 muscle, 1 endomyocardial and 1 sinus. Twenty-five of these 35 patients with PAN had histologically proven necrotizing vasculitis involving medium-sized vessels. Five of 6 patients with surgically removed abdominal organ tissue samples in the GI vasculitis group and all 41 patients with CA had histologically proven necrotizing vasculitis involving medium-sized vessels. Angiographic abnormalities were present in 26 of 30 patients with PAN who had angiography and in 12 of 14 patients with GI vasculitis who had angiography. All patients with abnormal angiograms in the GI vasculitis group and 81% in the PAN group demonstrated irregular arterial stenoses. Microaneurysms were observed in 75% of GI vasculitis and 73% in PAN. Pulse glucocorticoids (GC) were given to 3 (18%) patients with GI vasculitis and 7 (15%) patients with PAN. Only 2 (4%) patients with PAN were treated with plasmapheresis. Forty-five (94%) patients with PAN, 38 (93%) patients with CA and 12 (67%) patients with GI vasculitis were treated with oral GC. Mean (±SD) initial oral GC dose was 63.2±22.6 mg in PAN, 42.5±15.0 mg in CA and 61.7±10.3 mg in GI vasculitis group ($p<0.001$). Additional immunosuppressive agents were initiated at

baseline in 32 (67%) PAN, 7 (37%) GI vasculitis and 13 (32%) CA patients (p=0.002). Dapsone was used in 11 (27%) patients in CA group.

BVAS score was higher in patients with PAN than those with GI vasculitis or CA. The proportion of patients having FFS≥1 was higher in GI vasculitis compared to PAN group (58% vs. 42%, respectively; p<0.001; Table 2).

Follow-up characteristics and Relapses

Twenty-seven patients with PAN, 18 patients with CA and 9 patients with GI vasculitis were followed for at least 6 months. Mean (±SD) follow-up duration was 6.3±5.9 years in PAN group, 6.8±6.8 years in the CA and was 6.0±6.7 years in GI vasculitis group. Two patients in PAN and 3 patients in CA group never had clinical remission throughout the follow-up period in spite of different treatment approaches. The five-year cumulative rate of first relapse was 45.2% in CA, and only 9.6% in PAN group (Figure 1). During follow-up, there were 2 relapses in the PAN group (1 minor, 1 major) and 10 minor relapses in the CA group. The relapse rate was significantly higher in the CA group compared to PAN (10.5 vs 1.2 per 100 person-years; rate ratio: 7.15; 95% confidence interval [CI]:2.20, 45.16). There was no relapse in GI vasculitis group during follow-up.

Patients with CA were not receiving GC treatment during 6 of 10 relapses. Five of 10 relapses in the CA group developed while patients were on immunosuppressive therapy (2 methotrexate, 1 azathioprine, 1 mycophenolate mofetil, 1 sulfasalazine). One of 2 relapses in the PAN group developed despite GC treatment. Patients with PAN were not receiving additional immunosuppressives at the time of relapse. Relapses were generally treated with an increase in GC dose and/or change in immunosuppressive agent. The VDI score was comparable between PAN and GI vasculitis at the last follow-up, but was higher than CA (p=0.030; Table 3).

A total of 7 patients with PAN and 6 patients with GI vasculitis died during follow-up. The 1-, 5- and 10-year survival rates were 92.5%, 82.5% and 66.2% respectively in PAN, and 60.6%, 60.6% and 60.6%, respectively in GI vasculitis group (Figure 1). All deaths occurred within 1 year after diagnosis in GI vasculitis. Causes of death among the GI patients included uncontrolled vasculitis (n=2), unknown (n=2), cancer (n=1) and infection (n=1). Causes of death

among the PAN patients included cancer (n=2), uncontrolled vasculitis (n=1), and unknown (n=4). There were no deaths in CA group during the follow-up.

Potential predictors of relapse and mortality were assessed. The only characteristic significantly associated with development of the first relapse was CA diagnosis (HR: 5.07; 95% CI: 1.02 - 25.18). While lower BVAS score at baseline was also significantly associated with development of first relapse in a univariable model, it was no longer significant after adjustment for CA diagnosis (p=0.19). Mortality was significantly associated with older age (HR:1.05; 95% CI: 1.01 - 1.09), lower hemoglobin level (HR: 0.68; 95% CI: 0.48 - 0.94), presence of weight loss (HR: 13.79; 95% CI: 2.99 - 63.69), and arteriographic abnormalities (HR: 4.94; 95% CI: 1.35 - 18.07).

Further analysis was performed following the removal of patients with positive hepatitis serologies from the PAN group. With the exception of sex distribution no longer demonstrating significance (p=0.20) due to of 7 of 9 patients with hepatitis being male, no other changes were observed in the comparison of baseline characteristics, initial treatment or outcome (data not shown).

DISCUSSION

PAN is a necrotizing, systemic, medium-vessel vasculitis, typically without ANCA and rarely affects the lungs. These distinctive characteristics differentiate PAN from other vasculitides. CA and localized GI vasculitis are less well understood. While these conditions share similar histopathological findings with PAN, they appear to have distinct clinical courses.

The pathogenesis of PAN remains unknown. However, in a subset of patients, it may be associated with chronic HBV infection. In this series, most cases of PAN were idiopathic. There were 7 (15%) patients with hepatitis B and 2 (4%) with hepatitis C in the PAN group. HBV-related PAN was reported in up to 35.3% of patients in previous reports.[3] After successful vaccination against HBV, the rate of HBV-related PAN has decreased to less than 5% in developed countries.[16]

Progression from CA to systemic PAN appears to be exceedingly rare. Only 1 patient with CA evolved into systemic PAN during the disease course in the current cohort. Analogous findings

have been reported by Chen et al.[6] and Daoud et al[17] with 2 of 20 and 0 of 79 patients with CA, respectively, evolving into systemic PAN during follow-up. There are scarce data regarding vasculitis limited to the GI tract. In a report by Burke et al., 6 of 23 patients with isolated vasculitis of GI tract progressed to systemic PAN during follow-up.[18] In the present study, there was no progression to PAN among the patients with GI vasculitis.

Musculoskeletal and constitutional symptoms were common in the current systemic PAN cohort, as have been demonstrated by others.[3,19] Musculoskeletal symptoms (myalgia, arthralgia, leg tenderness) were also reported in over half of patients with CA. Symptoms among CA patients, however, were limited to extremities affected by vasculitic lesions and often secondary to reactive subcutaneous swelling and edema. The underlying cause of constitutional symptoms among patients with CA and GI vasculitis, as seen in this study and others,[18,19] is incompletely understood. A possibility includes systemic distribution of local inflammatory mediators leading to manifestations such as cytokine-associated fatigue. Indeed, symptoms such as fatigue were reported by nearly a quarter of patients with CA and GI vasculitis in this study. In isolation, constitutional symptoms were not able to differentiate the presence of a local versus systemic process.

Neurologic manifestations are frequently detected in systemic PAN. In the current series, 56% of patients with PAN described neurologic symptoms at diagnosis; the most common of which were peripheral neuropathy (27%) and mononeuritis multiplex (17%). While mononeuritis multiplex is considered a direct consequence of vasculitic neuropathy and a hallmark of underlying systemic disease, the presence of isolated sensory peripheral neuropathy is less specific. Indeed, studies have demonstrated 22-32% of patients with CA describe peripheral neuropathy at diagnosis without evidence of, or progression to, systemic PAN.[20,21] The etiology of such symptoms is unknown but may result from peripheral nerve compression due to extremity swelling as opposed to vasculitic pathology. Such was the case with the single patient in the CA group with mild sensory peripheral neuropathic symptoms described herein.

PAN is generally considered to be a monophasic disease with a low relapse rate ranging from 10% in HBV-related PAN[3] to 20-46% in idiopathic cases.[3, 22, 23] Although differences in clinical features and outcomes between those with HBV-related disease and idiopathic PAN have been observed, the low prevalence of HBV-related cases in the present cohort prevented direct comparison. In the current study, the five-year cumulative relapse rate was only 9.6% in the PAN group. The five-year cumulative relapse rate was 45.2% in CA and this was significantly higher compared with PAN. CA is a disease characterized by a chronic, relapsing course.[24] In the series by Daoud et al. 9 of 39 patients with ulcerative CA still had active cutaneous lesions after more 10 years of follow-up.[17] No relapses were observed in the GI vasculitis group in the current study population.

The development of a first relapse was significantly associated with a diagnosis of CA. While non-glucocorticoid immunosuppressive agents were used in 67% of patients with PAN, only 32% of patients with CA received initial treatment with immunosuppressive medications. Dapsone was preferred in around one fourth of CA by dermatologists in the current study. In routine practice, oral glucocorticoids with or without topical treatments are widely preferred by clinicians for patients with CA. There are few small case series showing efficacy of additional immunosuppressive therapies such as methotrexate[25] and intravenous immunoglobulin[26] in patients with cutaneous PAN resistant to high-dose glucocorticoid treatment. Less intense immunosuppressive therapy at diagnosis might be related to the high relapse rate seen in patients with CA.

In this study, the 1-, 5- and 10-year survival rates were 92.5%, 82.5% and 66.2% respectively in PAN, which is comparable to previous reports.[3] The survival rate in the first year after diagnosis was significantly reduced in GI vasculitis compared to PAN. In the series by Pagnoux et al. a FFS≥1, age >65 years, hypertension and GI manifestations requiring surgery were significantly associated with mortality.[3] Samson et al. reported an excellent overall survival rate of 86% at 96 months in patients with PAN without poor prognostic factors (FFS=0).[27] No association between FFS and mortality was detected in the current patient population. Mortality was significantly associated with older age, hemoglobin level, presence of weight loss, angiographic findings, gastrointestinal and cutaneous manifestations.

There is very limited literature on vasculitis-related damage in PAN. Samson et al. evaluated damage in PAN using the VDI score. The mean VDI score was 2.2 and most frequent sequelae were glucocorticoid related side effects such as osteoporosis, cataracts and peripheral neuropathy.[27] The VDI scores in the current series were similar to the findings of Samson et al. Hypertension and osteoporosis were the most frequent items of damage. As expected, in the present study, the VDI score was comparable between PAN and GI vasculitis groups, and lower among patients with CA.

The major limitation of this study is inherent to its retrospective design. Data collection relies on documentation by the treating physician at the time of clinical evaluation, which was not standardized. The relatively small sample size, lack of the follow-up data for all patients and relatively short term follow-up of patients are other significant limitations. Moreover, there are no validated assessment tools for definition of clinical activity, relapse or remission in medium vessel vasculitis.

In conclusion, these results suggest that systemic PAN, CA and GI vasculitis demonstrate different clinical courses, therefore suggesting they may be different conditions rather than a spectrum of the same disease. Progression of CA to systemic PAN is very rare. Vasculitis related damage is comparable between PAN and GI vasculitis. The risk of relapse is low in patients with PAN. Patients with CA have near a five-fold higher relapse rate compared to those with systemic PAN, possibly due to lower use of non-glucocorticoid immunosuppressive agents.

Table 1: Demographic and laboratory characteristics of patients with medium-sized vessel vasculitis at baseline according to type of vasculitic involvement

	Polyarteritis Nodosa (n=48)	Cutaneous Arteritis (n=41)	Gastrointestinal Vasculitis (n=19)	P value
Demographics				
Age at diagnosis, years*	52.8±15.8	49.1±18.8	52.6±15.7	0.65
Sex, male	29 (60%)	14 (34%)	8 (42%)	**0.041**
Race (n)				
White	35(95%)	32 (91%)	16 (94%)	
Black (African-American)	0	1(3%)	0	0.88
Other	2(6%)	2(6%)	1(6%)	
Number of ACR criteria met*	3.7±0.9	1.7±0.6	1.5±0.5	**<0.001**
Duration of symptoms (years)†	0.5(0.2-1.4)	0.8(0.3-1.7)	0.2(0-1.9)	0.11
Laboratory parameters				
White blood cell count (10^9/L)†	8.0 (6.2, 15.9)	7.1 (5.3, 10.6)	8.6 (6.0, 12.3)	0.18
Hemoglobin (g/dL)*	12.5±2.1	12.8±1.8	13.0±1.7	0.56
SedimentationRate (mm/hour) †	33.5 (9, 80)	30.0 (12, 49)	37.0 (10, 53)	0.73
C-reactive protein(mg/l)†	9.1(3-26)	10.1(2.9-33.1)	23.2(7.5-83)	0.22
Proteinuria(>400gm/24 hours)	5/44 (11%)	1/35(%3)	1/16(6%)	0.35
Hematuria	1/44(2%)	0/35 (0%)	1/15(7%)	0.32
Creatinine (mg/dl)*	1.0±0.4	0.9±0.2	1.0±0.3	0.92
Hepatitis B positivity (n)	7/46 (15%)	0/36 (0%)	0/17 (0%)	**0.013**
Hepatitis C positivity (n)	2/45 (4%)	0/34 (0%)	1/16 (6%)	0.40
Cryoglobulin positivity (n)	1/33 (3%)	0/29 (0%)	0/11 (0%)	0.54
c-ANCA positivity	0/41 (0%)	0/31 (0%)	0/15 (0%)	--
p-ANCA positivity	7/41(17%)	3/31 (10%)	0/15 (0%)	0.19
MPO-ANCA	0/26 (0%)	0/16 (0%)	0/8 (0%)	--
PR3-ANCA	0/26 (0%)	0/16 (0%)	0/8 (0%)	--

Values in bold statistically significant. *Mean ±SD †Median (Interquartile range); ACR: American College of Rheumatology

Table 2: Baseline clinical characteristics of patients with medium-sized vessel vasculitis according to type of vasculitic involvement

	Polyarteritis Nodosa (n=48)	Cutaneous Arteritis (n=41)	Gastrointestinal Vasculitis (n=19)	P value
Constitutional symptoms	34/48(71%)	13/41(32%)	12/19(63%)	**0.001**
Fever	12/48 (25%)	8/41 (20%)	3/19(16%)	0.66
Weight loss	22/48 (46%)	2/40 (5%)	8/19(42%)	**<0.001**
Fatigue	27/44(61%)	10/41(24%)	4/18(22%)	**0.001**
Musculoskeletal manifestations	33/48(69%)	22/41(54%)	2/19(11%)	**<0.001**
Myalgia/Weakness/Leg tenderness	33/48(69%)	9/41(22%)	1/19(5%)	**<0.001**
Arthralgia	15/47(32%)	17/41(41%)	2/19(11%)	0.057
Neurologic manifestations	27/48 (56%)	1/41 (2%)	0/19 (0%)	**<0.001**
Peripheral neuropathy	13/48(27%)	1/41 (2%)	0/19 (0%)	**<0.001**
Mononeuritis multiplex	8/48 (17%)	0/41(0%)	0/19 (0%)	**0.005**
Central nervous system involvement	6/48 (13%)	0/41(0%)	0/19 (0%)	**0.019**
Testicular pain/tenderness (men only)	5/29 (17%)	0/14(0%)	0/8 (0%)	0.12
Recent onset or severe hypertension	15/48 (31%)	0/41(0%)	3/19 (16%)	**<0.001**
Cutaneous Manifestations	27/48 (56%)	41/41(100%)	0/19 (0%)	**<0.001**
Ulcers	6/48 (13%)	6/41(15%)	0/19 (0%)	0.22
Nodules	11/48 (23%)	25/41 (61%)	0/19 (0%)	**<0.001**
Purpura	13/48 (27%)	13/41 (32%)	0/19 (0%)	**0.023**
Livedo reticularis	13/48 (27%)	16/41 (39%)	0/19 (0%)	**0.007**
Peripheral limb edema	9/47 (19%)	5/39 (13%)	0/19 (0%)	0.12
Gastrointestinal manifestations	20/48 (42%)	0/41(0%)	19/19 (100%)	**<0.001**
Abdominal pain	18/48 (38%)	0/41(0%)	17/19 (89%)	**<0.001**
Bleeding (Rectal or intraperitoneal)	5/48 (10%)	0/41(0%)	6/19 (32%)	**0.001**
Cholecystitis	0/48(0%)	0/41(0%)	2/19 (11%)	**0.008**
Pancreatitis	0/48(0%)	0/41(0%)	1/18 (5%)	0.094
GI manifestations requiring surgery	6/48 (13%)	0/41(0%)	6/19 (32%)	**0.001**
Cardiac involvement	1/48 (2%)	0/41(0%)	0/19(0%)	0.53

Vascular manifestations	3/48 (6%)	0/41 (0%)	0/19(0%)	0.145
Distal necrotic lesions	3/48 (6%)	0/41(0%)	0/19(0%)	0.14
Ophthalmologic involvement	2/47 (4%)	0/38(0%)	0/18(0%)	0.30
Pulmonary involvement	1/48 (2%)	0/41(0%)	0/19(0%)	0.53
Pleural effusions	1/48 (2%)	0/41(0%)	0/19(0%)	0.53
Ear Nose Throat involvement	1/44 (2%)	0/41(0%)	0/19(0%)	0.50
FFS=0	28/48 (58%)	41/41 (100%)	8/19 (42%)	
FFS=1	17/48 (35%)	0/41(0%)	11/19 (58%)	**<0.001**
FFS≥2	3/48 (6%)	0/41(0%)	0/19(0%)	
BVAS score at diagnosis*	12.1±4.9	2.4±1.2	9.0±2.8	**<0.001**

Values in bold statistically significant. GI:Gastrointestinal, FFS:Five Factor Score, BVAS: Birmingham Vasculitis Activity score. *Mean ±SD

Table 3: Treatment and damage assessment of patients with medium-sized vessel vasculitis according to type of vasculitic involvement

	Polyarteritis Nodosa (n=27)	Cutaneous Arteritis (n=18)	Gastrointestinal Vasculitis (n=9)	P value
Follow-up duration (years)*	6.3±5.9	6.8±6.8	6.0±6.7	--
Treatment, ever				
Oral glucocorticoids	27 (100%)	15 (83%)	8 (89%)	0.10
Cyclophosphamide	11 (41%)	0	2 (22%)	**0.007**
Methotrexate	1 (4%)	4 (22%)	2 (22%)	0.13
Azathioprine	4 (15%)	5 (28%)	1 (11%)	0.45
Mycophenolate mofetil	2 (7%)	3 (17%)	0	0.33
Treatment, last visit				
Oral glucocorticoids	12 (44%)	9 (50%)	3 (33%)	0.71
Prednisone dose, mg*	18.3±12.4	15.6±9.2	9.0±6.9	0.43
Other immunosuppressive agents	8 (30%)	9 (50%)	2 (22%)	0.25
VDI score†	2 (1-3)	0 (0-2)	2 (0-3)	**0.030**
VDI characteristics				
Musculoskeletal	12 (44%)	4 (22%)	5 (56%)	0.17
Skin/Mucous membranes	2 (77%)	4 (22%)	0	0.15
Ocular	1 (4%)	2 (11%)	2 (22%)	0.24
Cardiovascular	12 (44%)	4 (22%)	1 (11%)	0.103
Peripheral vascular disease	6 (22%)	2 (11%)	0	0.23
Gastrointestinal	3 (11%)	0	3 (33%)	**0.034**
Renal	6 (22%)	0	2 (22%)	0.096
Neuropsychiatric	4 (15%)	2 (11%)	0	0.47
Other	7 (26%)	0	3 (33%)	**0.041**

Values in bold statistically significant. VDI: Vasculitis Damage Index, *Mean ±SD †Median (Interquartile range)

Figure Legend

Figure 1. Survival (upper panel) and cumulative rate of first relapse (lower panel) of patients with medium-sized vessel vasculitis according to type of vasculitic involvement (Polyarteritis Nodosa [solid line], Cutaneous Arteritis [dashed line], and Gastrointestinal Vasculitis [dotted line]).

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Table 1: Demographic and laboratory characteristics of patients with medium-sized vessel vasculitis at baseline according to type of vasculitic involvement

	Polyarteritis Nodosa (n=48)	Cutaneous Arteritis (n=41)	Gastrointestinal Vasculitis (n=19)	P value
Demographics				
Age at diagnosis, years*	52.8±15.8	49.1±18.8	52.6±15.7	0.65
Sex, male	29 (60%)	14 (34%)	8 (42%)	**0.041**
Race (n)				
White	35(95%)	32 (91%)	16 (94%)	
Black (African-American)	0	1(3%)	0	0.88
Other	2(6%)	2(6%)	1(6%)	
Number of ACR criteria met*	3.7±0.9	1.7±0.6	1.5±0.5	**<0.001**
Duration of symptoms (years)†	0.5(0.2-1.4)	0.8(0.3-1.7)	0.2(0-1.9)	0.11
Laboratory parameters				
White blood cell count (10^9/L)†	8.0 (6.2, 15.9)	7.1 (5.3, 10.6)	8.6 (6.0, 12.3)	0.18
Hemoglobin (g/dL)*	12.5±2.1	12.8±1.8	13.0±1.7	0.56
SedimentationRate (mm/hour) †	33.5 (9, 80)	30.0 (12, 49)	37.0 (10, 53)	0.73
C-reactive protein(mg/l)†	9.1(3-26)	10.1(2.9-33.1)	23.2(7.5-83)	0.22
Proteinuria(>400gm/24 hours)	5/44 (11%)	1/35(%3)	1/16(6%)	0.35
Hematuria	1/44(2%)	0/35 (0%)	1/15(7%)	0.32
Creatinine (mg/dl)*	1.0±0.4	0.9±0.2	1.0±0.3	0.92
Hepatitis B positivity (n)	7/46 (15%)	0/36 (0%)	0/17 (0%)	**0.013**
Hepatitis C positivity (n)	2/45 (4%)	0/34 (0%)	1/16 (6%)	0.40
Cryoglobulin positivity (n)	1/33 (3%)	0/29 (0%)	0/11 (0%)	0.54
c-ANCA positivity	0/41 (0%)	0/31 (0%)	0/15 (0%)	--
p-ANCA positivity	7/41(17%)	3/31 (10%)	0/15 (0%)	0.19
MPO-ANCA	0/26 (0%)	0/16 (0%)	0/8 (0%)	--
PR3-ANCA	0/26 (0%)	0/16 (0%)	0/8 (0%)	--

Values in bold statistically significant. *Mean ±SD †Median (Interquartile range); ACR: American College of Rheumatology

Table 2: Baseline clinical characteristics of patients with medium-sized vessel vasculitis according to type of vasculitic involvement

	Polyarteritis Nodosa (n=48)	Cutaneous Arteritis (n=41)	Gastrointestinal Vasculitis (n=19)	P value
Constitutional symptoms	34/48(71%)	13/41(32%)	12/19(63%)	**0.001**
Fever	12/48 (25%)	8/41 (20%)	3/19(16%)	0.66
Weight loss	22/48 (46%)	2/40 (5%)	8/19(42%)	**<0.001**
Fatigue	27/44(61%)	10/41(24%)	4/18(22%)	**0.001**
Musculoskeletal manifestations	33/48(69%)	22/41(54%)	2/19(11%)	**<0.001**
Myalgia/Weakness/Leg tenderness	33/48(69%)	9/41(22%)	1/19(5%)	**<0.001**
Arthralgia	15/47(32%)	17/41(41%)	2/19(11%)	0.057
Neurologic manifestations	27/48 (56%)	1/41 (2%)	0/19 (0%)	**<0.001**
Peripheral neuropathy	13/48(27%)	1/41 (2%)	0/19 (0%)	**<0.001**
Mononeuritis multiplex	8/48 (17%)	0/41(0%)	0/19 (0%)	**0.005**
Central nervous system involvement	6/48 (13%)	0/41(0%)	0/19 (0%)	**0.019**
Testicular pain/tenderness (men only)	5/29 (17%)	0/14(0%)	0/8 (0%)	0.12
Recent onset or severe hypertension	15/48 (31%)	0/41(0%)	3/19 (16%)	**<0.001**
Cutaneous Manifestations	27/48 (56%)	41/41(100%)	0/19 (0%)	**<0.001**
Ulcers	6/48 (13%)	6/41(15%)	0/19 (0%)	0.22
Nodules	11/48 (23%)	25/41 (61%)	0/19 (0%)	**<0.001**
Purpura	13/48 (27%)	13/41 (32%)	0/19 (0%)	**0.023**
Livedo reticularis	13/48 (27%)	16/41 (39%)	0/19 (0%)	**0.007**
Peripheral limb edema	9/47 (19%)	5/39 (13%)	0/19 (0%)	0.12
Gastrointestinal manifestations	20/48 (42%)	0/41(0%)	19/19 (100%)	**<0.001**
Abdominal pain	18/48 (38%)	0/41(0%)	17/19 (89%)	**<0.001**
Bleeding (Rectal or intraperitoneal)	5/48 (10%)	0/41(0%)	6/19 (32%)	**0.001**
Cholecystitis	0/48(0%)	0/41(0%)	2/19 (11%)	**0.008**
Pancreatitis	0/48(0%)	0/41(0%)	1/18 (5%)	0.094
GI manifestations requiring surgery	6/48 (13%)	0/41(0%)	6/19 (32%)	**0.001**
Cardiac involvement	1/48 (2%)	0/41(0%)	0/19(0%)	0.53
Vascular manifestations	3/48 (6%)	0/41 (0%)	0/19(0%)	0.145
Distal necrotic lesions	3/48 (6%)	0/41(0%)	0/19(0%)	0.14
Ophthalmologic involvement	2/47 (4%)	0/38(0%)	0/18(0%)	0.30

Pulmonary involvement	1/48 (2%)	0/41(0%)	0/19(0%)	0.53
Pleural effusions	1/48 (2%)	0/41(0%)	0/19(0%)	0.53
Ear Nose Throat involvement	1/44 (2%)	0/41(0%)	0/19(0%)	0.50
FFS=0	28/48 (58%)	41/41 (100%)	8/19 (42%)	
FFS=1	17/48 (35%)	0/41(0%)	11/19 (58%)	**<0.001**
FFS≥2	3/48 (6%)	0/41(0%)	0/19(0%)	
BVAS score at diagnosis*	12.1±4.9	2.4±1.2	9.0±2.8	**<0.001**

Values in bold statistically significant. GI:Gastrointestinal, FFS:Five Factor Score, BVAS: Birmingham Vasculitis Activity score. *Mean ±SD

Table 3: Treatment and damage assessment of patients with medium-sized vessel vasculitis according to type of vasculitic involvement

	Polyarteritis Nodosa (n=27)	Cutaneous Arteritis (n=18)	Gastrointestinal Vasculitis (n=9)	P value
Follow-up duration (years)*	6.3±5.9	6.8±6.8	6.0±6.7	--
Treatment, ever				
Oral glucocorticoids	27 (100%)	15 (83%)	8 (89%)	0.10
Cyclophosphamide	11 (41%)	0	2 (22%)	**0.007**
Methotrexate	1 (4%)	4 (22%)	2 (22%)	0.13
Azathioprine	4 (15%)	5 (28%)	1 (11%)	0.45
Mycophenolate mofetil	2 (7%)	3 (17%)	0	0.33
Treatment, last visit				
Oral glucocorticoids	12 (44%)	9 (50%)	3 (33%)	0.71
Prednisone dose, mg*	18.3±12.4	15.6±9.2	9.0±6.9	0.43
Other immunosuppressive agents	8 (30%)	9 (50%)	2 (22%)	0.25
VDI score†	2 (1-3)	0 (0-2)	2 (0-3)	**0.030**
VDI characteristics				
Musculoskeletal	12 (44%)	4 (22%)	5 (56%)	0.17
Skin/Mucous membranes	2 (77%)	4 (22%)	0	0.15
Ocular	1 (4%)	2 (11%)	2 (22%)	0.24
Cardiovascular	12 (44%)	4 (22%)	1 (11%)	0.103
Peripheral vascular disease	6 (22%)	2 (11%)	0	0.23
Gastrointestinal	3 (11%)	0	3 (33%)	**0.034**
Renal	6 (22%)	0	2 (22%)	0.096
Neuropsychiatric	4 (15%)	2 (11%)	0	0.47
Other	7 (26%)	0	3 (33%)	**0.041**

Values in bold statistically significant. VDI: Vasculitis Damage Index, *Mean ±SD †Median (Interquartile range)

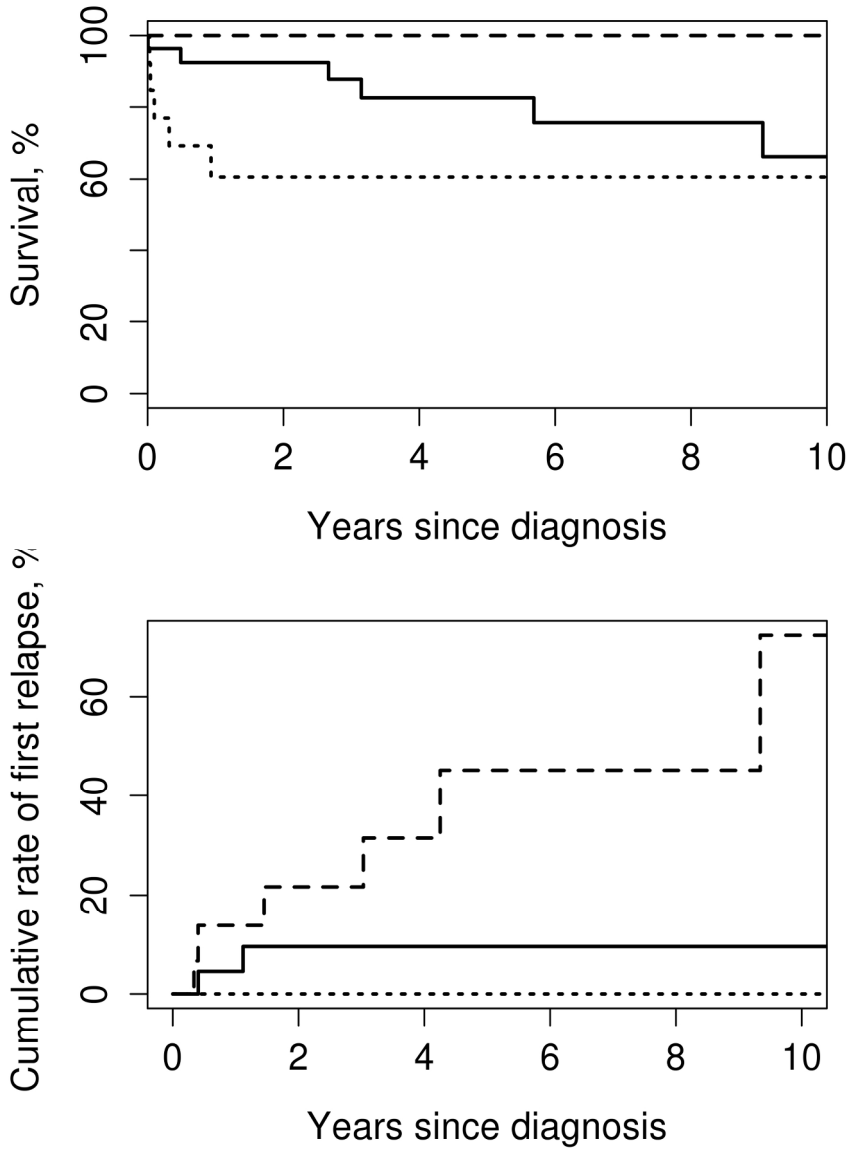

Figure 1. Survival (upper panel) and cumulative rate of first relapse (lower panel) of patients with medium-sized vessel vasculitis according to type of vasculitic involvement (Polyarteritis Nodosa [solid line], Cutaneous Arteritis [dashed line], and Gastrointestinal Vasculitis [dotted line]).

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