ORIGINAL ARTICLE

Clinical Spectrum of Medium-Sized Vessel Vasculitis

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Objective. 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 histopathologic 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, consisting 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. The disease of 1 patient evolved from CA 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 cases. The 5-year cumulative relapse rate was 45.2% in CA, and only 9.6% in PAN during a followup of approximately 6 years. No deaths were observed in the CA group. The survival rate at 10 years was 66% in the PAN group and 61% in the GI vasculitis group.

Conclusion. Systemic PAN, CA, and GI vasculitis take different clinical courses and therefore may be different diseases, rather than existing on a spectrum of the same disease. Progression of CA to systemic PAN is very rare. Relapse risk is low during followup in PAN. Patients with CA have a higher relapse rate than those with systemic PAN, possibly due to less use of immunosuppressive therapy in CA.

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 per 1 million adults (1,2). Skin and peripheral nervous system manifestations are the most common clinical findings, and glomerulonephritis is typically absent (3). Gastrointestinal manifestations are also frequently seen and are among the most important predictors of morbidity and mortality (4). A form of PAN limited to the skin, with no systemic involvement, was first defined as cutaneous PAN by

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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, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), and IgA vasculitis (7,8). The presence of GI manifestations in systemic vasculitis is associated with a worse prognosis (9). Vasculitis limited to the GI system is rarely 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) on the 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 on nomenclature, cutaneous PAN was 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).

Significance & Innovations

- Systemic polyarteritis nodosa (PAN), cutaneous arteritis (CA), and gastrointestinal (GI) vasculitis have different clinical courses and may be different diseases rather than on the spectrum of a single disease.

- The progression of CA to systemic PAN is very rare.

- Vasculitis-related damage is comparable in 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 than those with systemic PAN, possibly due to less use of immunosuppressive agents.

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.

PATIENTS AND METHODS

Patient population. A retrospective cohort study that included 108 patients evaluated at Mayo Clinic, Rochester, Minnesota, between January 1980 and December 2014 was performed. The longitudinal medical records of 1,515 patients were reviewed by a rheumatologist (FA-O). The review included all patients with the diagnostic code of polyarteritis nodosa (International Classification of Diseases, Ninth Revision, code 446.0), as well as all patients with the following key terms documented in their medical records: medium vessel vasculitis, mesenteric vasculitis, (localized) vasculitis of the GI tract, gallbladder vasculitis, periarteritis nodosa, testicular vasculitis, cutaneous polyarteritis nodosa, cutaneous arteritis, limited polyarteritis nodosa, PAN, and HBV-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-ANCA or myeloperoxidase-ANCA positivity were excluded. The study was approved by the Mayo Clinic Institutional Review Board.

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

Definitions. *Vasculitis on angiography.* This was defined as an 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.

PAN. The definition of PAN was based on the presence of ≥ 3 of the 10 items of the 1990 ACR 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).

SOV. The definition of SOV was 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 the 2012 CHCC definition (1). Necrotizing vasculitis limited to the GI system or 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.* This was assessed at all visits using the third version of the Birmingham Vasculitis Activity Score (BVAS), which rates 56 items derived from evaluations in 9 systems or organ groups (12). Remission was defined as the absence of disease activity attributable to vasculitis for ≥ 3 months (BVAS score 0). Relapse was defined as the recurrence of vasculitic manifestations (BVAS score >0), which required the addition of or a change in treatment with 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 the absence of clinical remission, occurrence of new vasculitic manifestation(s), or death before remission was achieved (13).

Prognosis. The prognostic Five-Factor Score (FFS), which includes parameters predictive of poorer outcome and mortality (creatinine >1.58 mg/dl, proteinuria >1 gm/24 hours, GI involvement, cardiomyopathy, and central nervous system 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 vasculitis-induced damage (15). For patients with followup, the VDI score was calculated at the last visit.

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's rank sum tests. Kaplan-Meier methods were used to estimate survival rates and the cumulative incidence of relapse in each group. Person-year calculations were used to determine relapse rates for each group, allowing for multiple relapses per patient. Rate ratios with 95% confidence intervals (95% CIs) were calculated, assuming the occurrence of relapses followed a 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, and R, version 3.1.1, 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 1990 ACR criteria but met the CHCC definition for PAN. This patient was included in the PAN group based on expert opinion (study authors). There was only 1 patient with CA whose disease activity evolved into systemic PAN during the disease course. While there was a male predominance in the 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 HBV surface antigen positivity, and 2 patients had hepatitis C virus antibody (anti-HCV) positivity. Viral DNA was detected in 5 of 7 patients with HBV positivity. Viral RNA was detected in both patients with HCV 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. In the GI vasculitis group, 1 patient had HCV.

Four of 7 PAN patients with HBV positivity were treated with antiviral agents together with immunosuppressive therapy. Two patients did not receive antiviral treatment, due to the absence of viremia. There were missing data regarding HBV treatment for 1 patient. Two patients with PAN and 1 patient with GI vasculitis with HCV positivity were not treated with antiviral agents during the course of this study.

At disease onset, the most common clinical features in the PAN group were constitutional (n = 34, 71%), musculoskeletal (n = 33, 69%), neurologic (n = 27, 56%), and cutaneous manifestations (n = 27, 56%). 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 nonvasculitic, 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 shown 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

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

Characteristic	PAN (n = 48)	CA (n = 41)	GI vasculitis (n = 19)	P
Demographics				
Age at diagnosis, mean ± SD years	52.8 ± 15.8	49.1 ± 18.8	52.6 ± 15.7	0.65
Male, no. (%)	29 (60)	14 (34)	8 (42)	0.041†
Race, no. (%)				0.88
White	35 (95)	32 (91)	16 (94)	
Black	0 (0)	1 (3)	0 (0)	
Other	2 (6)	2 (6)	1 (6)	
ACR criteria met, mean ± SD	3.7 ± 0.9	1.7 ± 0.6	1.5 ± 0.5	< 0.001†
Duration of symptoms, median (IQR) 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/liter), median (IQR)	8.0 (6.2–15.9)	7.1 (5.3–10.6)	8.6 (6.0–12.3)	0.18
Hemoglobin, mean ± SD gm/dl	12.5 ± 2.1	12.8 ± 1.8	13.0 ± 1.7	0.56
Sedimentation rate, median (IQR) mm/hour	33.5 (9–80)	30.0 (12–49)	37.0 (10–53)	0.73
C-reactive protein, median (IQR) mg/liter	9.1 (3–26)	10.1 (2.9–33.1)	23.2 (7.5–83)	0.22
Proteinuria (>400 gm/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, mean ± SD mg/dl	1.0 ± 0.4	0.9 ± 0.2	1.0 ± 0.3	0.92
HBV positivity	7/46 (15)	0/36 (0)	0/17 (0)	0.013†
HCV positivity	2/45 (4)	0/34 (0)	1/16 (6)	0.40
Cryoglobulin positivity	1/33 (3)	0/29 (0)	0/11 (0)	0.54
Classic ANCA positivity	0/41 (0)	0/31 (0)	0/15 (0)	–
Perinuclear 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 are the number/total number (%) unless otherwise indicated. PAN = polyarteritis nodosa; CA = cutaneous arteritis; GI = gastrointestinal; ACR = American College of Rheumatology; IQR = interquartile range; HBV = hepatitis B virus; HCV = hepatitis C virus; ANCA = antineutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3.
† Statistically significant.

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

Characteristic	PAN (n = 48)	CA (n = 41)	GI vasculitis (n = 19)	P
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 extremity edema	9/47 (19)	5/39 (13)	0/19 (0)	0.12
GI 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				< 0.001†
0	28/48 (58)	41/41 (100)	8/19 (42)	
1	17/48 (35)	0/41 (0)	11/19 (58)	
≥2	3/48 (6)	0/41 (0)	0/19 (0)	
BVAS score at diagnosis, mean ± SD	12.1 ± 4.9	2.4 ± 1.2	9.0 ± 2.8	< 0.001†

* Values are the number/total number (%) unless otherwise indicated. PAN = polyarteritis nodosa; CA = cutaneous arteritis; GI = gastrointestinal; FFS = Five Factor Score; BVAS = Birmingham Vasculitis Activity Score.
† Statistically significant.

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 the GI vasculitis group and in 73% of the PAN group. Pulse glucocorticoids (GCs) were given to 3 patients (18%) with GI vasculitis and 7 patients (15%) with PAN. Only 2 patients with PAN (4%) were treated with plasmapheresis. Forty-five patients (94%) with PAN, 38 patients (93%) with CA, and 12 patients (67%) with GI vasculitis were treated with oral GCs. The mean ± SD initial oral GC dose was 63.2 ± 22.6 mg in the PAN group, 42.5 ± 15.0 mg

in the CA group, and 61.7 ± 10.3 mg in the GI vasculitis group (*P* < 0.001). Additional immunosuppressive agents were initiated at baseline in 32 PAN patients (67%), 7 GI patients (37%), and 13 CA patients (32%) (*P* = 0.002). Dapsone was used in 11 patients (27%) in the CA group. BVAS scores were higher in patients with PAN than in those with GI vasculitis or CA. The proportion of patients with FFS ≥1 was higher in the GI vasculitis group than in the PAN group (58% versus 42%, respectively; *P* < 0.001) (Table 2).

Followup 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 followup duration was 6.3 ± 5.9 years in the PAN group, 6.8 ± 6.8 years in the CA group, and 6.0 ± 6.7 years in the GI vasculitis group. Two patients in the PAN group and 3
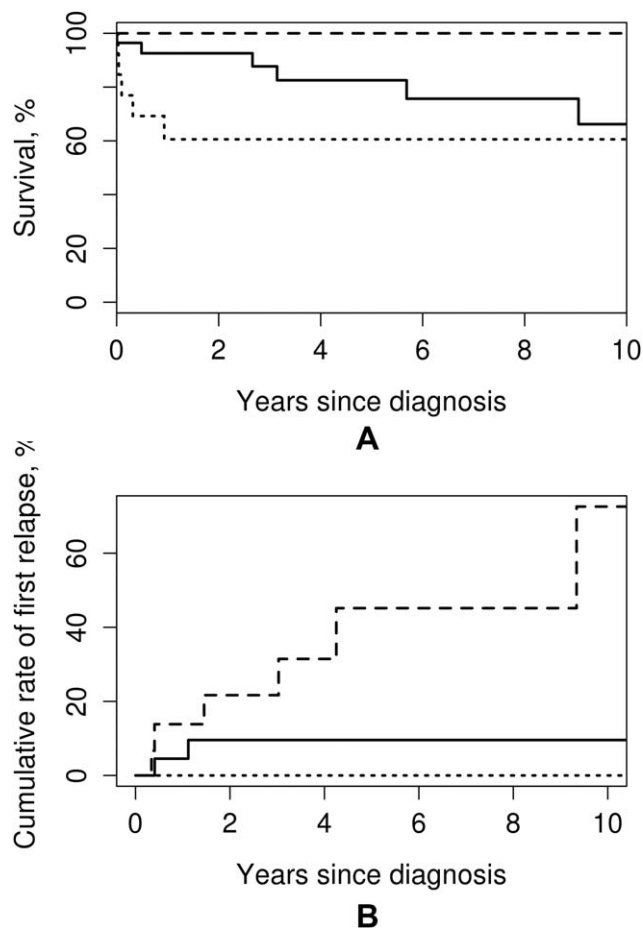
Figure 1. A, Survival rate and **B,** cumulative rate of first relapse of patients with medium-sized vessel vasculitis according to type of vasculitic involvement: polyarteritis nodosa (solid line), cutaneous arteritis (broken line), and gastrointestinal vasculitis (dotted line).

patients in the CA group never had clinical remission throughout the followup period, in spite of different treatment approaches. The 5-year cumulative rate of first relapse was 45.2% in the CA group and only 9.6% in the PAN group (Figure 1). During followup, there were 2 relapses in the PAN group (1 minor and 1 major) and 10 minor relapses in the CA group. The relapse rate was significantly higher in the CA group compared to the PAN group (10.5 versus 1.2 per 100 person-years; rate ratio 7.15 [95% CI 2.20–45.16]). There were no relapses in the GI vasculitis group during followup.

Patients with CA were not receiving GC treatment in 6 of the 10 relapses. Five of 10 relapses in the CA group developed while patients were receiving immunosuppressive therapy (2 methotrexate, 1 azathioprine, 1 mycophenolate mofetil, and 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 a change in immunosuppressive agent. The VDI score was comparable between the PAN and GI vasculitis groups at the last followup, but was higher than that of the CA group (*P* = 0.030) (Table 3).

A total of 7 patients with PAN and 6 patients with GI vasculitis died during followup. The 1-, 5-, and 10-year survival rates were 92.5%, 82.5%, and 66.2%, respectively, in the PAN group and 60.6% at all 3 time points in the GI vasculitis group (Figure 1). All deaths occurred within 1 year after diagnosis in the GI vasculitis group. Causes of death among the GI patients were uncontrolled vasculitis (n = 2), unknown (n = 2), cancer (n = 1), and infection (n = 1). Causes of death among the PAN patients were cancer (n = 2), uncontrolled vasculitis (n = 1), and unknown (n = 4). There were no deaths in the CA group during the followup.

Potential predictors of relapse and mortality were assessed. The only characteristic significantly associated with the development of the first relapse was CA diagnosis (hazard ratio [HR] 5.07 [95% CI 1.02–25.18]). A lower BVAS score at baseline was also significantly associated with the development of the first relapse in a univariable model; however, 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]), 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 7 of the 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 AAV and rarely affecting the lungs. These distinctive characteristics differentiate PAN from other vasculitides. CA and localized GI vasculitis are less well understood. While these conditions share similar histopathologic 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 patients (15%) with HBV and 2 (4%) with HCV in the PAN group. HBV-related PAN was reported in up to 35.3% of patients in a previous report (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. There was only 1 patient in this cohort whose CA evolved into systemic PAN during the disease course. Analogous findings have been reported by Chen (6) and Daoud et al (17), with the disease of 2 of 20 and 0 of 79 patients with CA, respectively, evolving into systemic PAN during followup. There are scarce data regarding vasculitis limited to the GI tract. In a report by Burke et al, the disease of 6 of 23 patients with isolated vasculitis of the GI tract progressed to systemic PAN during followup (18). In the present study, there were no cases of progression from GI vasculitis to PAN.

Musculoskeletal and constitutional symptoms were common in the current systemic PAN cohort, as in others (3,9).

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

	PAN (n = 27)	CA (n = 18)	GI vasculitis (n = 9)	*P*
Followup duration, mean ± SD 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)	0.33
Treatment, last visit				
Oral glucocorticoids	12 (44)	9 (50)	3 (33)	0.71
Prednisone dose, mean ± SD 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, median (IQR)	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)	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)	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)	0.47
Other	7 (26)	0	3 (33)	0.041†

* Values are the number (%) unless otherwise indicated. PAN = polyarteritis nodosa; CA = cutaneous arteritis; GI = gastrointestinal; VDI = Vasculitis Damage Index; IQR = interquartile range.
† Statistically significant.

Musculoskeletal symptoms (myalgia, arthralgia, leg tenderness) were also reported in more than half of patients with CA. Symptoms among patients with CA, 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 (9,18), is not fully understood. One possibility is the 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, we could not use constitutional symptoms to differentiate between a local versus a 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 that 22–32% of patients with CA describe peripheral neuropathy at diagnosis without evidence of, or progression to, systemic PAN (19,20). 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 (3,9,21). 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 5-year cumulative relapse rate was only 9.6% in the PAN group. The 5-year cumulative relapse rate was 45.2% in the CA group, which was significantly higher than that in the PAN group. CA is a disease characterized by a chronic, relapsing course (22). In the series by Daoud et al, 9 of 39 patients with ulcerative CA still had active cutaneous lesions after more than 10 years of followup (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-GC 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 by dermatologists in approximately one-fourth of the CA patients in the current study. In routine practice, oral GCs with or without topical treatments are widely preferred by clinicians for patients with CA. There are few small case series showing the efficacy of additional immunosuppressive therapies such as methotrexate (23) and

intravenous immunoglobulin (24) in patients with cutaneous PAN resistant to high-dose GC 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 are comparable to previous reports (3). The survival rate in the first year after diagnosis was significantly lower in GI vasculitis than in PAN. In the series by Pagnoux et al, an 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 score 0) (25). No association between FFS and mortality was detected in this patient population. Mortality was significantly associated with older age, hemoglobin level, weight loss, angiographic findings, and gastrointestinal and/or cutaneous manifestations. There is very limited literature on vasculitis-related damage in PAN. Samson et al evaluated damage in PAN using VDI scores. The mean VDI score was 2.2, and the most frequent sequelae were GC-related side effects, such as osteoporosis, cataracts, and peripheral neuropathy (25). The VDI scores in the current series were similar to the findings by Samson et al. Hypertension and osteoporosis were the most frequent items. As expected, in the present study, the VDI score was comparable between the PAN and GI vasculitis groups, and lower among patients with CA.

The major limitation of this study is inherent in 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 followup data on all patients, and relatively short-term followup of patients are other significant limitations. Moreover, there are no validated assessment tools that define clinical activity, relapse, or remission in medium vessel vasculitis.

In conclusion, these results suggest that systemic PAN, CA, and GI vasculitis have different clinical courses, which suggests that they may be different conditions rather than exist on the spectrum of a single disease. The progression of CA to systemic PAN is very rare. Vasculitis-related damage is comparable in PAN and GI vasculitis. The risk of relapse is low in patients with PAN. Patients with CA have nearly a 5-fold higher relapse rate than those with systemic PAN, possibly due to less use of non-GC immunosuppressive agents.

AUTHOR CONTRIBUTIONS

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