Original article

Clinical characteristics in patients with myalgia as the initial manifestation of small and medium-sized vasculitis: a retrospective study

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Running title: Myalgia in small and medium-sized vasculitis

Abstract

Myalgia is a common symptom in small and medium-sized systemic vasculitis, sometimes occurring as the initial or only clinical manifestation of vasculitis. This study investigated the clinical features and diagnostic process in patients presenting with myalgia as the initial symptom of anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) or polyarteritis nodosa (PAN). We included 93 patients diagnosed with AAV or PAN by retrospectively reviewing their clinical records at initial diagnosis. Clinical findings and diagnostic methods were assessed in patients with myalgia. Of 93 patients, myalgia was observed in 21 (22.6%) patients, with diagnostic classifications of microscopic polyangiitis (MPA) in 12 (52.4%), granulomatosis with polyangiitis in 2 (9.5%), eosinophilic granulomatosis with polyangiitis in 2 (9.5%), and PAN in 5 (23.8%). Myalgia was present in the lower extremities of all patients; more than 80% of patients had pain in the calf muscle. In 10 patients with myalgia, including 7 with MPA and 3 with PAN, muscle biopsy was performed because myalgia was the main symptom and no other impaired organs were suitable for biopsy. Consequently, 8 patients had necrotizing vasculitis, leading to MPA or PAN diagnosis, although muscle pathology was not evaluated in patients without myalgia. Muscle magnetic resonance imaging was useful in determining the biopsy site. Myalgia, especially in the lower limbs, may be an initial clinical sign of vasculitis, particularly in MPA or PAN patients. Moreover, the histological evidence of muscular vasculitis can contribute to a definite diagnosis especially in patients presenting with myalgia as an early symptom

of AAV or PAN.

Keywords: Myalgia, ANCA-associated vasculitis, polyarteritis nodosa, microscopic polyangiitis

Compliance with ethical standards

The authors declare that they have no financial or personal conflicts of interest.

The present study was approved by the Local Ethics Committee of Shinshu University (approved number 614 and 3907), and informed consent was obtained from all participants.

Funding: none

Acknowledgements

We wish to thank the members of the Department of Medicine (Neurology and Rheumatology) for their efforts in providing medical care. We would like to thank Editage (www.editage.com) for English language editing.

Contributions

Diagnosis and medical care were performed by all authors. S-U, K-U, and D-M made muscle biopsy specimens. Y-Shi conceived of and designed this study. Y-Shi, S-U, D-K analyzed the data. Y-Shi and S-U prepared the draft of this manuscript. Y-Shi and Y-Se revised the manuscript. All authors approved the final manuscript and agreed to be responsible for all aspects of this study.

Introduction

Primary systemic vasculitis (PSV) is an autoimmune inflammatory disorder that affects several types of vessels, including the arteries, capillaries, and veins, and leads to impairments of the organs they serve. Small-sized vessel vasculitis (SVV) and medium-sized vessel vasculitis (MVV) result in ischemic, hemorrhagic, and inflammatory impairments of surrounding tissues based on the infiltration of destructive inflammatory cells. While SVV and MVV share the histological features of necrotizing vasculitis in the absence of immune-complement deposition, they are separately categorized into anti-neutrophil cytoplasmic antibody (ANCA)-vasculitis (AAV), or polyarteritis nodosa (PAN), respectively. AAV is further classified into three categories: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. Both AAV and PAN can be life-threatening because of severe visceral disorders; however, musculoskeletal involvement is a common general symptom of patients with AAV or PAN [2-4]. Notably, in PAN, muscular involvement sometimes occurs as the initial clinical manifestation of vasculitis [5-9], suggesting that muscular symptoms have a key role in MVV and SVV. In this study, we aimed to investigate the clinical characteristics of patients presenting with myalgia as the main symptom in the early phase of AAV and PAN, as well as their diagnostic process.

Methods

Patients and study design

The clinical records of 102 patients with AAV or PAN who were admitted to our hospital between September 2006 and October 2019 were reviewed. The diagnosis and classification of MPA, GPA, EGPA, and PAN were determined according to the criteria of the Chapel Hill Consensus Conference (CHCC) [1] and/or the consensus algorithm proposed by the European Medicines Agency (EMA algorithm) [10]. We excluded patients who had complications of neoplasm and infections, those who had insufficient clinical information for the definite diagnosis and/or the study analyses, and those in whom the diagnosis of AAV or PAN was impossible to differentiate from other diseases. Consequently, 93 patients were included in this study (mean age, 62 years; 35 men and 58 women). Of the 93 patients, 40 (43.0 %), 19 (20.4 %), 13 (14.0 %), and 21 (22.6 %) were diagnosed with MPA, GPA, EGPA, and PAN, respectively. The epidemiological and clinical features at the initial diagnosis of AAV or PAN were investigated in patients who demonstrated myalgia (with myalgia) and were statistically compared to those of patients who did not demonstrate myalgia (without myalgia). In accordance with the Birmingham Vasculitis Activity Score version 3 (BVAS), myalgia was defined as pain in the muscles [11,12].

Physical and laboratory assessments

Laboratory measurements retrieved from clinical records included white blood cell (WBC) count, serum levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), creatine kinase (CK),

positivity for myeloperoxidase-ANCA and proteinase 3-ANCA. The disease activity and related symptoms based on BVAS [12] were also evaluated. The localization of myalgia, which was recorded by the physicians after their direct medical examination, was categorized into the neck, upper extremities (proximal or distal), and lower extremities (proximal or distal). In magnetic resonance imaging (MRI) screening of the targeted muscle, a hyper-intensity signal on the short-tau inversion recovery (STIR) image was considered a significant "positive" finding. When the biopsied muscle tissue indicated the presence of necrotizing vasculitis compatible with the CHCC criteria [1], histological evaluation was determined as "definite." Neuropathy was diagnosed following the observation of abnormal findings of motor or sensory nerve conduction velocities.

Statistical analyses

Categorical variables are presented as the mean ± standard deviation. The statistical analyses were performed using JMP (SAS Institute, Cary, USA) and Bell Curve for Excel (SSRI, Tokyo, Japan). The normality test was used to determine the distribution of the obtained data. The Mann-Whitney U test and Chi-squared test of independence were used to compare data from independent groups, and the Steel-Dwass test was performed for multiple comparisons. *P*-values less than 0.05 were considered statistically significant.

Results

Epidemiologic and clinical findings in patients with and without myalgia

Of 93 patients, myalgia was present in 21 (22.6%); 12 (57.1%), 2 (9.5%), 2 (9.5%), and 5 (23.8%) of whom were classified as MPA, GPA, EGPA, and PAN, respectively (**Table 1**). The prevalence of myalgia was relatively higher in MPA (12/40 [30.0%]) and PAN (5/21 [23.8%]) than in GPA (2/19 [10.5%]) and EGPA (2/13 [15.4%]). Nevertheless, the differences were not statistically significant (data not shown). BVAS was significantly lower in patients with myalgia than those without myalgia (p = 0.0034). As for the other symptoms associated with vasculitis, the frequency of arthritis was significantly higher in patients with myalgia than those without myalgia (p = 0.0178). A significantly lower frequency of neurological involvement was demonstrated in patients with myalgia than those without myalgia (p = 0.0185); notably, the mononeuritis multiplex was significantly less prevalent (p = 0.0129). One patient with myalgia who indicated mononeuritis multiplex was diagnosed with MPA following sural nerve biopsy. Neither ANCA-positive phenotypes nor laboratory findings revealed significant differences between patients with and without myalgia. Three patients with myalgia, whose diagnosis was MPA, EGPA, and PAN, demonstrated increased serum CK levels (580 U/L, 307 U/L, and 926 U/L, respectively), while only 1 PAN patient without myalgia demonstrated elevated serum CK levels (410 U/L). Consequently, the frequency of elevated serum CK levels was significantly higher in patients with myalgia (14.3%) than those without myalgia (1.4%) (p = 0.0348). Meanwhile, among patients with myalgia who showed normal serum CK levels, serum aldolase levels were also

normal (3.61 ± 1.41 U/L [range 1.9−5.7 U/L], normal <6.1 U/L).

The distribution of myalgia in patients with PSV

With regards to the distribution of myalgia, the lower extremities were involved in all patients (**Table 2**), resulting in a significantly higher frequency of myalgia in the lower extremities than in the neck or upper extremities ($p < 0.0001$, $p = 0.0011$, respectively) (**Table 3**). In particular, myalgia in the distal lower legs, including the calves, was significantly higher (85.7%) than that in the neck or distal upper extremities ($p < 0.0001$). In patients with MPA, frequency of myalgia in the lower extremities was significantly higher than in the neck or upper extremities ($p = 0.0007$, $p = 0.0174$, respectively); moreover, the frequency of myalgia in the distal lower extremities was significantly higher than in the neck or the distal upper extremities ($p = 0.0440$, $p = 0.0135$, respectively) (**Supplementary table**). Patients with PAN significantly presented with myalgia in the lower extremities than in the neck ($p = 0.0111$).

Clinical features and muscle biopsy in patients with myalgia

Among patients who exhibited myalgia, the mean BVAS was relatively, but non-significantly, lower in patients with EGPA and PAN (7.6 ± 1.5 and 6.2 ± 4.1, respectively) than those with MPA and GPA (13.7 ± 7.3 and 17.0 ± 7.1, respectively). The 2 patients with GPA demonstrated involvement of the ear, nose, and throat (100%); incidence of this was significantly lower in MPA (8.3%) ($p = 0.0359$) (**Fig. 1**). As such, nasal mucosa was ultimately used for the histopathological examination in GPA.

Meanwhile, muscle biopsy of either the gastrocnemius or quadriceps femoris muscle was performed in seven patients with MPA, and three with PAN because of the absence of other suitable sites for the biopsy (**Table 4**). Muscle MRI before the biopsy showed increased STIR signals in all patients. One patient with PAN, who was diagnosed by skin biopsy instead of muscle biopsy, also revealed increased signals in the gastrocnemius muscle (data not shown). Consequently, the muscular compartments showing high-intensity signals on MRI were determined as the target for biopsy (**Fig. 2**). The histopathological findings of biopsied tissue indicated necrotizing vasculitis compatible with the CHCC criteria in five patients with MPA (71.4%), and in three with PAN (100%). Meanwhile, perivascular inflammatory cell infiltration without fibrinoid necrosis, which was insufficient for indicating necrotizing vasculitis, was demonstrated in two patients who were eventually classified with MPA through the surrogate markers of urine described in the EMA algorithm [10]. All 10 patients showed neither myonecrosis nor cellular infiltration in the muscle fibers. Of the seven patients with MPA who underwent muscle biopsy, four indicated asymptomatic pulmonary infiltration, three had microscopic proteinuria and/or hematuria with normal levels of serum creatinine and glomerular filtration rate, one demonstrated sensory neuropathy, and one showed sensorineural deafness. The mean BVAS of these patients was significantly lower than the remaining five MPA patients with myalgia (8.6 ± 2.4 vs. 20.8 ± 5.5, $p = 0.0041$).

Discussion

In the present study, patients with myalgia were significantly associated with higher frequency of arthritis than those without myalgia. This supported that myalgia, similar to arthritis, may occur as the initial manifestation of PSV and that they may co-manifest [4]. Cases with muscular manifestations in the lower extremities, typically of the calf muscle, have been reported as muscular vasculitis related to PAN or PAN-mimicking disorders [5-9,13,14]. In our series of 21 patients with myalgia, the lower extremities were involved in all of them, and calf muscle pain was demonstrated in more than 80% of patients. Consequently, either the gastrocnemius or quadriceps femoris muscle was selected for biopsy. Muscle biopsy was performed in patients with myalgia who lacked a suitable visceral impairment site for biopsy, as well as a lower BVAS than other patients, suggesting that muscle biopsy would be useful as a definite diagnostic procedure even in the early phase of SVV and MVV. Muscular impairments of the lower limbs have been described as a localized and/or initial symptom of PAN [5,13,14], whereas the present study demonstrated that muscular vasculitis in the lower limbs could be a crucial early indication of MPA. To the best of our knowledge, only three cases of AAV have been reported in which muscular symptoms were the initial and main manifestation of disease and whereby definite diagnosis was made by muscle biopsy [15-17]. However, of the eight patients whose histology of biopsied muscle fulfilled the CHCC criteria in our study, five (62.5%) were classified as MPA. In addition, the prevalence of MPA in all patients presenting with myalgia was more than 50% at the

initial diagnosis. Accordingly, it is essential to focus on myalgia as a common and key manifestation for the early diagnosis of MPA. Previous studies have demonstrated the usefulness of muscle biopsy for detecting SVV and/or MVV, including all types of PSV [18,19]. Muscles, especially those of the lower limbs, may be suitable targets for the histological diagnosis of early phase AAV and PAN, even in the absence of typical visceral manifestations.

Of the 10 patients who underwent muscle biopsy in the present study, eight demonstrated definite histological findings of necrotizing vasculitis, involving small- or medium-sized arteries with fibrinoid necrosis with inflammatory cell infiltration. The sensitivity of muscle biopsy for the diagnosis of necrotizing vasculitis has been widely described to range between 33–88% in patients with PSV [18-20]. In our patients, the biopsy site was determined based on the MRI findings, as signal changes are useful for screening the presence of vasculitis [13,14,21]. Thus, muscle MRI may increase diagnostic sensitivity by acting as a guide for selection of the biopsy site. Furthermore, muscle MRI is useful for differentiating muscular vasculitis from referred pain because of arthritis; especially when a higher frequency of arthritis was demonstrated in patients with myalgia than those without myalgia in the present study. Although muscle MRI is also useful in the screening of inflammatory myositis (IM), the pathological mechanism underlying musculoskeletal involvement in IM has been found to be different from that in SVV or MVV. The pathological feature of IM is necrosis and/or the inflammatory destruction of muscle fibers leading to the elevation of serum CK levels [22]. On the other hand, it is

well-established that abnormal signal intensity on muscle MRI in SVV or MVV is induced by the edematous changes of muscle tissues from reversible ischemia ascribable to vasculitis [7,21,23]. This non-destructive response within muscle fibers would also result in normal or mild increased serum CK levels. In fact, our patients presenting with elevated serum CK levels immediately showed improvement of CK levels after treatment initiation (data not shown), whereas patients with IM require a longer duration in achieving normalization of serum CK levels [24]. In addition, we demonstrated the absence of serum aldolase elevation in patients presenting with normal levels of serum CK, supporting this pathological mechanism. Meanwhile, typical necrotizing vasculitis is not always correlated with abnormal MRI signals [13,14]. Indeed, non-necrotizing vasculitis localized in the calf muscle has also been reported as PAN-like vasculitis [14], and the incidence of typical necrotizing vasculitis has been found to be 50% in AAV or PAN patients presenting with muscular vasculitis [18]. In this study, two patients with MPA, whose diagnosis was ultimately determined based on surrogate markers, demonstrated insufficient histology, which was perivascular inflammation without fibrinoid necrosis. However, despite histologic insufficiency, it is necessary to detect any evidence of vasculitis to achieve definite diagnosis as early as possible, because of the possibility of long-term localized AAV developing into the generalized type during its clinical course [25]. Therefore, we expect that muscle biopsy based on MRI screening could contribute to the prompt diagnosis of muscular vasculitis in the early phase of disease. Moreover, the detection of muscular vasculitis could provide an

opportunity to start appropriate immunosuppressive treatment for preventing advanced impairment.

This study has some limitations. First, this was a retrospective study involving the review of a limited number of patient clinical records. Because of the lack of data on muscular vasculitis in patient's without myalgia as a control group, it was ultimately impossible to demonstrate the precise prevalence of muscular vasculitis in AAV and PAN. Moreover, muscle biopsy was performed in only a limited number of patients with myalgia despite the biopsy-proven findings shown in eight patients. Second, it might be difficult to precisely discriminate myalgia from neuropathic pain because the latter is also the most representative symptom of vasculitic sensory neuropathy [26]. Third, there were concerns that some patients may lack myalgia even if muscular vasculitis occurs. In fact, previous studies have demonstrated that the frequency of myalgia was 40–50% even in patients whose biopsied muscle tissue clearly indicated vasculitis [19,20]. The coexistence of muscular vasculitis and vasculitic neuropathy has been described, and concomitant biopsy of the sural or peroneal nerve together with the gastrocnemius muscle increases the diagnostic sensitivity of vasculitis [26,27]. Moreover, 75% of patients diagnosed with vasculitic neuropathy concomitantly revealed muscular vasculitis [19]. Given these previous investigations, it was hypothesized that muscular vasculitis may asymptomatically occur in some patients because of differences in pain thresholds. Furthermore, the present study showed that the frequency of mononeuritis multiplex was significantly higher in patients without myalgia than those with myalgia, which might have resulted in the lower BVAS in patients with

myalgia than those without myalgia. Thus, it may be required to consider the possibility of asymptomatic muscular vasculitis in patients with motor nerve palsies. In addition, we assumed that concomitant presentation of vasculitic neuropathy and muscular vasculitis predominantly indicated neuropathic pain with obvious innervations rather than myogenic pain.

In conclusion, myalgia, especially in the lower limbs, may be an early clinical sign of MVV and SVV, predominantly in PAN and MPA. Preliminary screening by muscle MRI can be useful as a guide for determining the appropriate biopsy site, while the histological evidence of muscular vasculitis can contribute to the prompt and definite diagnosis of AAV or PAN, especially in patients presenting with myalgia as the early symptom of disease.

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Figure legends

Fig. 1 Clinical manifestations in patients presenting with myalgia

Comparison of patients diagnosed with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and polyarteritis nodosa (PAN). ENT: ear, nose, and throat. ※Significantly higher frequency in GPA than MPA ($p < 0.05$).

Fig. 2 Representative MRI images and histological findings of muscle

MRI image shows hyper-intensity on short-tau inversion recovery. The pathology specimens stained with hematoxylin and eosin demonstrate necrotizing vasculitis. MRI of the distal lower leg was performed in case 3, 7, and 8 (**a, b,** and **c**, respectively), and of the proximal lower leg in case 9 (**d**). The muscle biopsy was taken from the gastrocnemius muscle in case 3, 7, and 8 (**e, f**, and **g**, respectively), and from the quadriceps femoris muscle in case 9 (**h**). Scale bar is 100 μm.

MRI: magnetic resonance imaging

Table 1 Clinical findings in patients with and without myalgia

	With myalgia (n = 21)	**Without myalgia (n = 72)**	***p* value***
Male : female	8:13	27:45	0.6238
Age, year	63 ± 14	62 ± 16	0.6490
Classification of vasculitis			
MPA (%)	12 (52.4)	28 (37.5)	0.1085
GPA (%)	2 (9.5)	17 (22.2)	0.1334
EGPA (%)	2 (9.5)	11 (13.9)	0.3961
PAN (%)	5 (23.8)	16 (22.2)	0.5448
BVAS	11.8 ± 7.0	17.2 ± 7.7	**0.0034**
Symptoms			
Fever (%)	14 (66.7)	43 (59.7)	0.3784
Arthritis (%)	10 (47.6)	15 (20.8)	**0.0178**
Weight loss	3 (14.3)	18 (25.0)	0.2357
Cutaneous (%)	4 (19.0)	27 (37.5)	0.0916
Mucous membrane and eyes (%)	0	8 (11.1)	0.1175
ENT (%)	3 (14.3)	22 (30.6)	0.1125
Pulmonary (%)	10 (47.6)	35 (48.6)	0.5671
Cardiovascular (%)	1 (4.8)	6 (8.3)	0.5248
Abdominal (%)	1 (4.8)	6 (8.3)	0.5018
Renal (%)	8 (38.1)	41 (56.9)	0.4419
Nervous system (%)	8 (38.1)	48 (66.7)	**0.0185**
Headache (%)	2 (9.5)	12 (16.7)	0.3381
Seizure (%)	0	4 (5.6)	0.3524

Cerebrovascular event (%)	0	5 (6.9)	0.2692
Cranial neuropathy, total (%)	2 (9.5)	15 (20.8)	0.1987
Sensory peripheral neuropathy (%)	6 (28.6)	36 (50.0)	0.0672
Mononeuritis multiplex (%)	3 (14.3)	31 (43.1)	**0.0129**
Laboratory data			
MPO-ANCA (%)	11 (52.3)	41 (56.9)	0.5367
PR3-ANCA (%)	2 (9.5)	9 (12.5)	0.5275
WBC, /μL	12492 ± 8217	11296 ± 4745	0.7652
CRP, mg/dL	10.0 ± 7.2	7.1 ± 6.8	0.0596
ESR, mm/h	77 ± 31	62 ± 37	0.3127
CK, U/L	113 ± 228	58 ± 58	0.2802
Increased CK‡, n (%)	3 (14.3)	1 (1.4)	**0.0348**

MPA: Microscopic polyangiitis, GPA: Granulomatosis with polyangiitis, EGPA: Eosinophilic granulomatosis with polyangiitis, PAN: Polyarteritis nodosa, BVAS: the Birmingham Vasculitis Activity Score, ENT: ear, nose, and throat, MPO: Myeloperoxidase, PR3: Proteinase 3, ANCA: Anti-neutrophil cytoplasmic antibody, WBC: White blood cell, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, CK: Creatine kinase. ‡More than normal values (>165 U/L). Data are shown as mean ± SD (standard deviation). *Comparison between patients with and without myalgia (<0.05 is considered to be statistically significant).

Table 2 Distribution of myalgia in patients with MPA, GPA, EGPA, or PAN

	Total (n = 21)	**MPA** (n = 12)	**GPA** (n = 2)	**EGPA** (n = 2)	**PAN** (n = 5)
Neck (%)	3 (14.3)	3 (25.0)	0	0	0
Upper extremities, total (%)	11 (52.4)	6 (50.0)	1 (50.0)	1 (50.0)	3 (60.0)
Proximal	10 (47.6)	5 (41.7)	1 (50.0)	1 (50.0)	3 (60.0)
Distal	3 (14.3)	2 (16.7)	0	0	1 (20.0)
Lower extremities, total (%)	21 (100)	12 (100)	2 (100)	2 (100)	5 (100)
Proximal	13 (61.9)	5 (41.7)	2 (100)	2 (100)	4 (80.0)
Distal	18 (85.7)	10 (83.3)	2 (100)	2 (100)	4 (80.0)

MPA: Microscopic polyangiitis, GPA: Granulomatosis with polyangiitis, EGPA: Eosinophilic granulomatosis with polyangiitis, PAN: Polyarteritis nodosa.

Table 3 Statistical comparison of myalgia distribution in all patients presenting with myalgia (n = 21)

		Neck	Upper extremities (Proximal + Distal)
Upper extremities	Proximal + Distal	0.0237	—
Lower extremities	Proximal + Distal	<0.0001	0.0011

		Neck	Upper extremities		Lower extremities (Proximal)
			Proximal	Distal	
Upper extremities	Proximal	0.1471	—	—	—
	Distal	1.0000	0.1471	—	—
Lower extremities	Proximal	0.0153	0.8954	0.0153	—
	Distal	<0.0001	0.0756	<0.0001	0.4232

p-values are indicated in the table. < 0.05 is statistically significant.

Table 4 Evaluations associated with skeletal muscle impairment in patients who underwent muscle biopsy

Case	Age	Gender	Diagnosis	BVAS	CK† (U/L)	ALD♯ (U/L)	Myalgia*		Muscle biopsy		MRI findings		Visceral involvement
							Proximal	Distal	Portion	Histology‡	quadri	gastro	
1	57	F	MPA	6	40	1.9	−	+	gastro	definite	NP	positive	P
2	69	M	MPA	9	73	5.5	−	+	gastro	definite	NP	positive	P, R
3	76	F	MPA	6	37	2.1	+	+	gastro	definite	NP	positive	P
4	70	F	MPA	9	33	2.2	−	+	gastro	insufficient	NP	positive	R
5	76	F	MPA	9	10	5.7	+	+	quadri	definite	positive	positive	N
6	77	F	MPA	13	15	5.3	+	+	gastro	insufficient	NP	positive	A, P, R
7	82	F	MPA	8	39	5.6	−	+	gastro	definite	NP	positive	Sd
8	66	F	PAN	3	12	2.4	+	+	gastro	definite	NP	positive	ND
9	61	M	PAN	10	926	12.0	+	+	quadri	definite	positive	NP	A, R
10	59	F	PAN	2	58	4.3	+	+	gastro	definite	NP	positive	A

BVAS: The Birmingham Vasculitis Activity Score, MPA: Microscopic polyangiitis, PAN: Polyarteritis nodosa; gastro: Gastrocnemius muscle; quadri, Quadriceps femoris muscle, NP: Not performed, A: Arthritis, P: Pulmonary, R: Renal, N: Neuropathy, Sd: sensorineural deafness, ND: Not demonstrated. CK†: Serum levels of creatine kinase (normal: <165 U/L), ALD♯: serum levels of aldolase (normal: <6.1 U/L).

‡Compatible with the CHCC criteria. *In the lower extremities.

Fig. 1

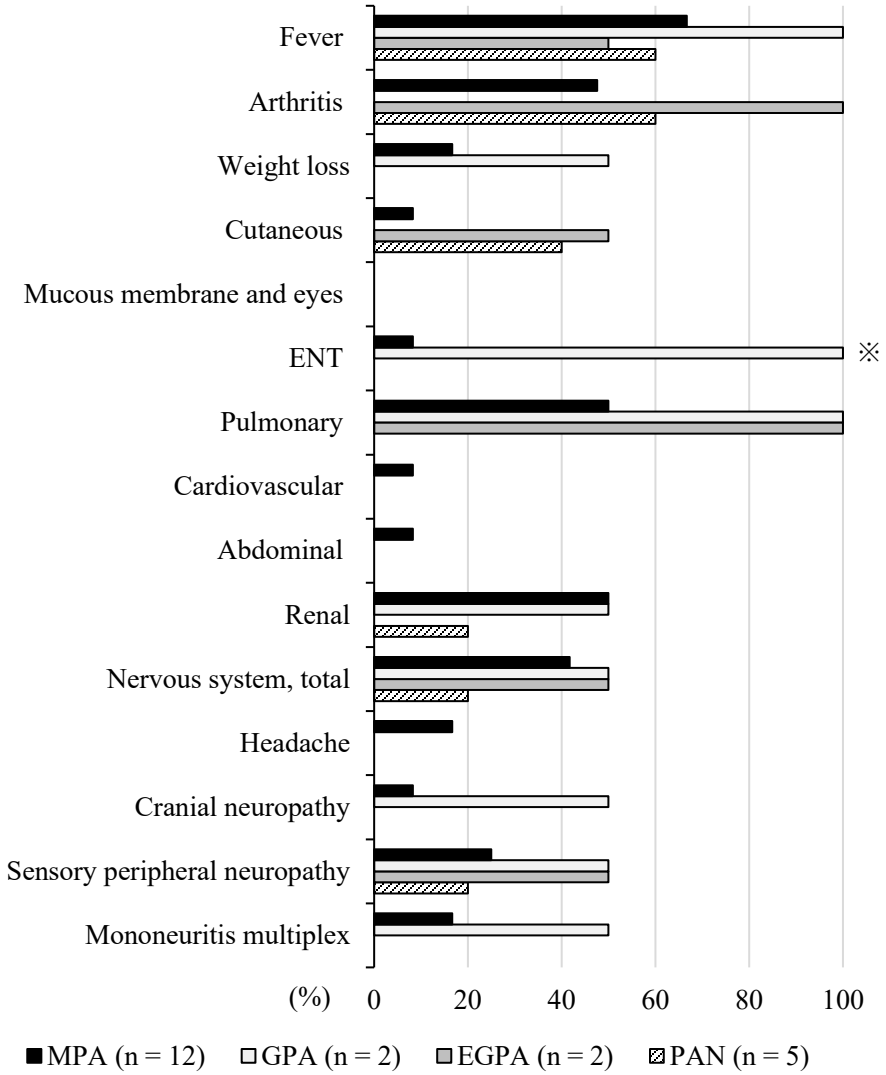
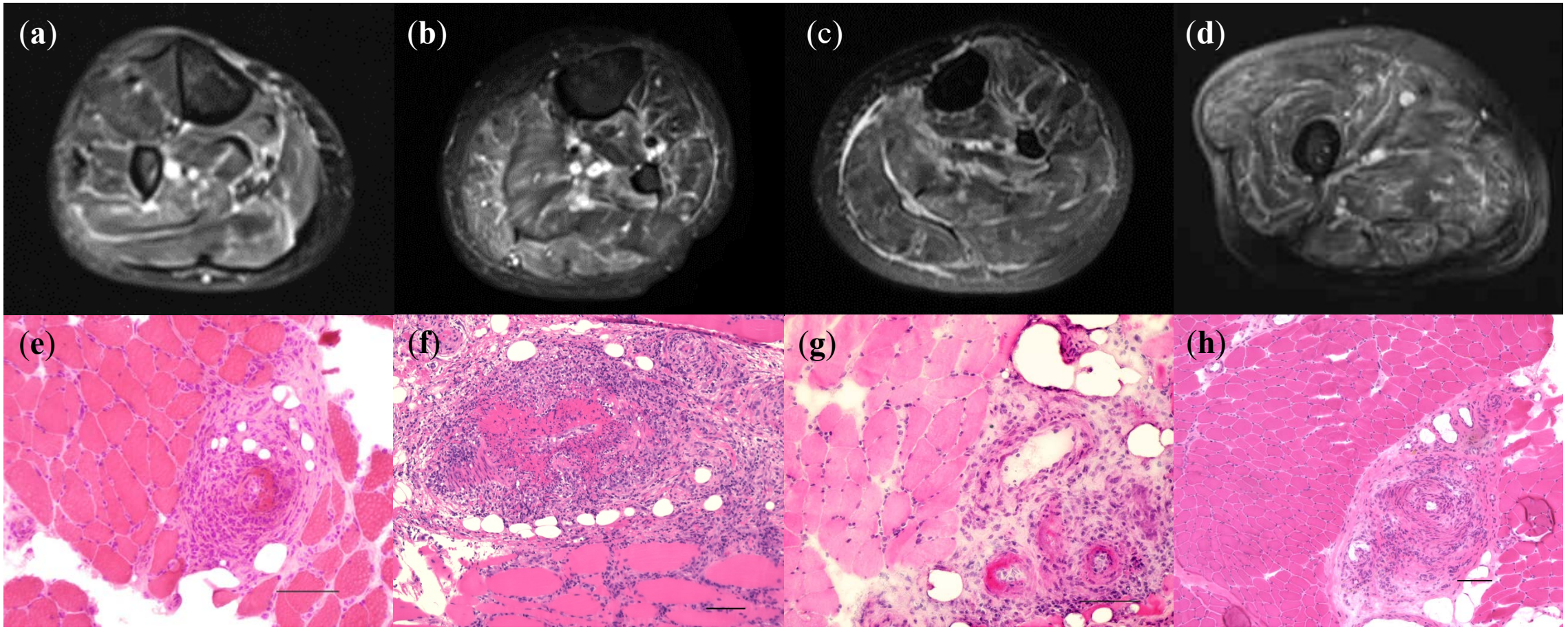

Fever
Arthritis
Weight loss
Cutaneous
Mucous membrane and eyes
ENT
※
Pulmonary
Cardiovascular
Abdominal
Renal
Nervous system, total
Headache
Cranial neuropathy
Sensory peripheral neuropathy
Mononeuritis multiplex
(%)
0
20
40
60
80
100
MPA (n = 12)
GPA (n = 2)
EGPA (n = 2)
PAN (n = 5)

Fig. 2



Supplementary Table 1 Statistical comparison of myalgia distribution in patients with MPA

		Neck	Upper extremities (Proximal + Distal)
Upper extremities	Proximal + Distal	0.4508	—
Lower extremities	Proximal + Distal	0.0007	0.0174

		Neck	Upper extremities		Lower extremities
			Proximal	Distal	(Proximal)
Upper extremities	Proximal	0.9269	—	—	—
	Distal	0.9915	0.7022	—	—
Lower extremities	Proximal	0.9269	1.0000	0.7022	—
	Distal	0.0440	0.2518	0.0135	0.2518

MPA: microscopic polyangiitis. *p*-values are indicated in the table. < 0.05 is statistically significant.

Supplementary Table 2 Statistical comparison of myalgia distribution in patients with GPA

		Neck	Upper extremities (Proximal + Distal)
Upper extremities	Proximal + Distal	0.8713	—
Lower extremities	Proximal + Distal	0.3957	0.8713

		Neck	Upper extremities		Lower extremities
			Proximal	Distal	(Proximal)
Upper extremities	Proximal	0.9874	—	—	—
	Distal	1.0000	0.9874	—	—
Lower extremities	Proximal	0.6918	0.9874	0.6918	—
	Distal	0.6918	0.9874	0.6918	1.0000

GPA: granulomatosis with polyangiitis. *p*-values are indicated in the table. < 0.05 is statistically significant.

Supplementary Table 3 Statistical comparison of myalgia distribution in patients with EGPA

		Neck	Upper extremities (Proximal + Distal)
Upper extremities	Proximal + Distal	0.8713	—
Lower extremities	Proximal + Distal	0.3957	0.8713

		Neck	Upper extremities		Lower extremities
			Proximal	Distal	(Proximal)
Upper extremities	Proximal	0.9874	—	—	—
	Distal	1.0000	0.9874	—	—
Lower extremities	Proximal	0.6918	0.9874	0.6918	—
	Distal	0.6918	0.9874	0.6918	1.0000

EGPA: eosinophilic granulomatosis with polyangiitis. *p*-values are indicated in the table. < 0.05 is statistically significant.

Supplementary Table 4 Statistical comparison of myalgia distribution in patients with PAN

		Neck	Upper extremities (Proximal + Distal)
Upper extremities	Proximal + Distal	0.1588	—
Lower extremities	Proximal + Distal	0.0111	0.3675

		Neck	Upper extremities		Lower extremities
			Proximal	Distal	(Proximal)
Upper extremities	Proximal	0.3544	—	—	—
	Distal	0.9307	0.8054	—	—
Lower extremities	Proximal	0.1363	0.9850	0.4464	—
	Distal	0.1363	0.9850	0.4464	1.0000

PAN: polyarteritis nodosa. *p*-values are indicated in the table. < 0.05 is statistically significant.