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Provisional seven-item criteria for the diagnosis of polyarteritis nodosa

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Abstract

Polyarteritis nodosa (PAN) is a potentially life-threatening systemic vasculitis, which predominantly involves medium arteries. However, it may be difficult to diagnose PAN in its early stage. The aim of our study was to investigate the sensitivity and specificity of the American College of Rheumatology (ACR) and the Japanese Ministry of Health, Labour and Welfare (MHLW) criteria for the diagnosis of PAN in a single-centre retrospective cohort in Japan and to develop simplified criteria with favourable diagnostic performance. All patients with "PAN" or "suspicion of PAN," as indicated on insurance forms, were included. The patient population was classified into PAN and non-PAN groups based on a retrospective chart review. The sensitivity and specificity of the ACR and MHLW criteria were calculated. Items that favourably discriminated the PAN group from the non-PAN group were determined and used as items for our provisional criteria. Thirteen cases of PAN and 24 cases without PAN were included in this study. The sensitivities of the ACR and MHLW criteria were 61.5% (8/13) and 30.8% (4/13), respectively, whereas the specificities were 79.2% (19/24) and 87.5% (21/24), respectively. We developed provisional criteria consisting of seven items, and found that a cut-off of ≥ 4 items had a sensitivity of 92.3% (12/13) and specificity of 91.7% (22/24) ($p < 0.000001$). The provisional seven-item criteria, developed in our real-world cohort of patients suspected of having PAN, had a high sensitivity and specificity and may be useful in the diagnosis of PAN, although it should be validated in additional patient populations.

Keywords Polyarteritis nodosa · Criteria · Sensitivity · Specificity · Seven-item criteria

Introduction

Polyarteritis nodosa (PAN) is a rare type of systemic vasculitis, defined as necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with anti-neutrophil cytoplasmic antibody (ANCA) [1]. Although it may be difficult to diagnose PAN in its early stages, delayed therapy may result in life-threatening conditions, such as bowel perforation or aneurysm rupture [2]. The American College of Rheumatology (ACR) 1990 criteria for classification of PAN had a sensitivity and specificity of 82.2% and 86.6%, respectively [3, 4]. However, the criteria were derived from clinical data in cases with an established diagnosis of PAN during an era in which microscopic polyangiitis (MPA) was not recognized as a distinct entity from PAN. When the ACR criteria were used for diagnostic purposes, the sensitivity decreased to 41–50% [5, 6]. In Japan, the diagnostic criteria of the Ministry of Health, Labour and Welfare (MHLW) for PAN were revised in 2006 [7]. However, no studies investigating the diagnostic performance of the criteria have been published. Our study aimed to (1) investigate the sensitivity and specificity of the ACR and MHLW criteria from a single-centre patient cohort with suspicion of PAN, and (2) develop simplified criteria with a favourable diagnostic performance.

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Materials and methods

The database of electronic charts was used to determine the patient population with any suspicion of PAN. All patients who visited our hospital between January 2000 and October 2019 and had received a diagnosis of PAN or were suspected of having PAN based on medical insurance forms were included in this study. In Japan, doctors are required to provide a disease name for insurance purposes at the patient's first visit when they order any tests or prescriptions. Accordingly, we regarded those with insurance records that included "PAN" or "s/o PAN" as having a suspicion of PAN in the clinical setting. Inclusion criterion for the PAN group was a diagnosis based on our retrospective review. Patients not meeting this criterion were included in the non-PAN group. The classification of vasculitis in our study population was also evaluated with the European Medicines Agency (EMEA) algorithm [8].

A retrospective chart review was performed for both groups. The following data from before initiating therapy were extracted for analysis: age, sex, diagnosis, follow-up period, fever ≥ 38 °C and its duration, C-reactive protein level, erythrocyte sedimentation rate, urine protein assessed using the dipstick test (described as ±, 1 +, 2 +, or 3 +), urine red blood cell (RBC) count, expressed as the number per high-power field (HPF), myeloperoxidase (MPO)-ANCA (usually on an enzyme-linked immunosorbent assay, or "peripheral pattern" on immunofluorescence staining in old cases), as well as 10 items for the ACR criteria and 12 items for the MHLW criteria. Among items from the MHLW criteria, hypertension was defined as systolic BP > 140 mmHg or diastolic BP > 90 mmHg, and skin ulcers included protracted wound healing after skin biopsy. Arterial abnormalities compatible with PAN on contrast-enhanced computed tomography or magnetic resonance angiography were considered a positive finding for an arteriographic abnormality for both ACR and MHLW criteria.

Based on the extracted data, the sensitivity and specificity of the ACR and MHLW criteria were calculated. We then developed provisional criteria with the most favourable diagnostic performance in our study population. Using a 2 × 2 table for each item, we calculated sensitivity, specificity, and + likelihood ratio (LR) and analysed the association of each item with the diagnosis of PAN. The duration of fever was subclassified as ≥ 1 week, ≥ 10 days, and ≥ 2 weeks, and combined with "weight loss" using "OR" or "AND" to achieve a better performance. Cutaneous lesions were subclassified into livedo reticularis (or livedo racemosa), subcutaneous nodules, skin ulcer, gangrene, and purpura, and were similarly combined with each other. MPO-ANCA, urine protein < 1 +, < 2 +, urine RBC < 5/HPF, and < 10/HPF were also evaluated. Our criteria consisted of several items that are possibly associated with PAN ($p < 0.2$) and that have a high sensitivity or + LR; one point was allotted to each item as was done for the ACR criteria, whereas histological and angiographic findings were included as one of our criteria based on their approved role in the diagnosis of PAN [3, 7, 8]. Finally, we determined the appropriate number of items and the cut-off value of the total points.

Statistical analysis

Categorical variables were compared between groups using Fisher's exact test. Continuous variables were compared with Student's *t* test or the Mann–Whitney *U* test, as appropriate. Missing data on clinical manifestations (i.e., weight loss) were regarded as "negative." Missing data on hypertension, hepatitis B surface antigen or antibody, ANCA, urine protein, and urine RBC were excluded from the analysis. In a receiver operating characteristics (ROC) curve analysis, the cut-off point closest to the top-left corner of the ROC square was selected [9]. The threshold of $p < 0.05$ was considered statistically significant. All analyses were conducted using EZR [10].

Results

Study population

Our study population included 37 patients. Thirteen and 24 cases were included in the PAN and non-PAN groups, respectively (Supplementary dataset). Clinical data except for MPO-ANCA did not differ significantly between groups (Table 1). According to the EMEA algorithm, of the 13 PAN cases, 7 were classified based only on histological findings, 1 was classified based on both angiographic and histological findings, and 1 was classified based only on angiographic findings. Although one case presenting with intractable leg ulcers and mononeuropathy multiplex (MM) could be classified as MPA based on small vessel vasculitis, we considered this case as having PAN rather than MPA because of the absence of MPO-ANCA or glomerulonephritis [1]. The remaining three were judged as "unclassifiable," but none of them had glomerulonephritis or MPO-ANCA. All of the three "unclassifiable" cases had MM. Two of them also had ischemic gastrointestinal lesions, while the remaining case had livedo reticularis.

Twenty-four patients in the non-PAN group were finally diagnosed with MPA ($n = 7$), cutaneous polyarteritis nodosa (cPAN) ($n = 6$), livedo vasculitis ($n = 3$), unclassified cutaneous vasculitis, eosinophilic granulomatosis with polyangiitis (EGPA), immune-mediated necrotizing myopathy,

Table 1 Clinical characteristics of the PAN and non-PAN groups

	PAN ($n=13$)	Non-PAN ($n=24$)	p values
Age, mean (SD)	56.9 (13.2)	56.5 (19.7)	N.S
Sex (male:female)	7:6	11:13	N.S
CRP (mg/dl), median (range)*	5.59 (0.062–15.06)	2.53 (0.019–39.31)	N.S
ESR (mm/1 h), median (range)*	50 (10—> 110)*	50 (3—> 110)*	N.S
FUP (days), median (range)	1111 (118—6274)	881 (21–4285)	N.S
	Positive/negative	Positive/negative	
MPO/peripheral ANCA, n	0/13	7/17	< 0.05
Urine RBC ≥ 5/HPF, n	3/9	7/13	N.S
Urine protein ≥ 1 + , n	1/12	6/16	N.S

PAN polyarteritis nodosa, *N.S.* not significant, *CRP* C reactive protein, *IQR* interquartile range, *ESR* erythrocyte sedimentation rate, *FUP* follow-up period, *MPO* myeloperoxidase, *ANCA* anti-neutrophil cytoplasmic antibody, *RBC* red blood cell, *HPF* high-power field

*An upper limit of measurement of ESR was "> 110". This value was replaced by "111" for statistical analysis (Supplementary dataset)

intra-abdominal haemorrhage due to dissection of the supramesenteric artery, recurrent meningitis, s/o IgA vasculitis, chronic inflammatory demyelinating polyneuropathy, and fever of unknown origin ($n=1$ each) (Supplementary dataset). All seven cases with MPA had MPO-ANCA, whereas five of them had glomerulonephritis, and the remaining two had MM with purpura or livedo reticularis. Six cases had cPAN, while "livedo vasculitis" was found in three cases; this term was conventionally used by dermatologists to mean the cutaneous lesions of livedo reticularis or racemosa without histological evidence of cPAN.

Sensitivity and specificity of the two criteria

Clinical items and their diagnostic performance are listed in Supplementary Table 1. When applying the ACR criteria to the PAN group, eight cases were classified as having PAN. When applying the MHLW criteria, four cases were classified as "definite" or "probable or definite" PAN. Thus, the sensitivity of the ACR and MHLW criteria (definite or probable) was 61.5% (8/13), and 30.8% (4/13), respectively. For the non-PAN group, five and three cases were misclassified as PAN through the ACR and MHLW criteria, respectively. Thus, the specificity of the ACR and MHLW criteria was 79.2% (19/24) and 87.5% (21/24), respectively. The ACR criteria, but not the MHLW criteria, had a significant association with the diagnosis of PAN ($p<0.05$ and $p>0.20$, respectively) (Supplementary Table 1).

Development of provisional diagnostic criteria for PAN

Each item was analysed for its association with the diagnosis of PAN (Table 2, Supplementary Table 1). "Mononeuropathy or polyneuropathy", MM, gastrointestinal involvement, and absence of MPO-ANCA were, by

Table 2 Association of items with the diagnosis of PAN

	PAN Positive/negative (Sensitivity)	Non-PAN Positive/negative (Specificity)	Positive LR	p values (Fisher's test)
MM	9/4 (69.2%)	5/19 (79.2%)	3.32	< 0.01
Gastrointestinal involvement	3/10 (23.1%)	0/24 (100%)	∞	< 0.05
Absence of ANCA	13/0 (100%)	17/7 (29.2%)	1.41	< 0.05
UP < 2 +	13/0 (100%)	17/5 (22.7%)	1.29	0.13
Fever for 1 week OR weight loss ≥ 4 kg	8/5 (61.5%)	9/15 (62.5%)	1.64	0.18
Angiographic abnormality	2/11 (15.4%)	1/23 (95.8%)	3.69	N.S
Biopsy for the ACR	8/5 (61.5%)	10/14 (58.3%)	1.48	N.S

ACR American College of Rheumatology, *ANCA* anti-neutrophil cytoplasmic antibody, *LR* likelihood ratio, *MM* mononeuropathy multiplex, *PAN* polyarteritis nodosa, *UP* urine protein, *N.S.* not significant

themselves, significantly associated with a diagnosis of PAN. We selected MM as a neurological item for our criteria because of a higher + LR. Urine protein < 2 + had a sensitivity of 100% with a possible association with PAN ($p = 0.13$). When combining weight loss ≥ 4 kg with fever for ≥ 1 week, "fever for 1 week OR weight loss of ≥ 4 kg" had a sensitivity of 67.7% ($p = 0.16$). According to the predetermined rule, the histological and angiographic findings of PAN were included as an item (although neither reached statistical significance). For histological findings, we selected the definition of the ACR, "granulocyte or mixed leukocyte infiltrate in an arterial wall on biopsy," because of its higher sensitivity (61.5%).

As a result, our provisional criteria consisted of seven items (Table 3). The cut-off value ≥ 4 for the total of the items (1 point for each) had a sensitivity of 92.3% (12/13) and a specificity of 91.7% (22/24) (12 of 13 in PAN versus 2 of 24 in non-PAN group, $p < 0.000001$) (Supplementary Table 2). Only one false-negative finding was seen in a PAN case, presenting with livedo reticularis and gangrene, that subsequently had MM and histological evidence of PAN. Similarly, two false-positive findings were noted in one EGPA case with PAN-like features and another case of intra-abdominal haemorrhage due to the dissection of the supra mesenteric artery. We also tested 17 other models consisting of 6 or 7 items, in which 1–3 points were allotted for each item according to its association with PAN and + LR (Supplementary Table 2), but no other models achieved as good a performance as the 7-item criteria (1 point for each). Accordingly, we concluded that four of the seven items had the most favourable diagnostic performance in our study population.

Discussion

This is the first study to develop diagnostic criteria for PAN in a real-world cohort of patients suspected of having PAN. Our provisional seven-item criteria had a sensitivity of 92.3% and specificity of 91.7%. As suggested in a previous review [11], we included the absence of ANCA as an item in our criteria and also included abnormalities of the visceral arteries on contrast-enhanced computed tomography and magnetic resonance angiography as angiographic abnormalities. The provisional seven-item criteria may be used for diagnostic purposes, whenever PAN is suspected, because these criteria were derived from clinical data before treatment.

In recent clinical practice management of suspected PAN, an experienced physician would promptly plan biopsies of symptomatic sites (i.e., skin or muscle) or contrast-enhanced computed tomography, determining when to start glucocorticoid therapy based on the likelihood of PAN. Ideally, such therapy should follow a definitive diagnosis, but a delay in therapy may lead to poor outcome in certain cases of emergent visceral involvement. Furthermore, the clinical diagnosis of PAN should be based on the physician's experience and the definition of PAN, because there are no diagnostic criteria for PAN. The ACR 1990 criteria for classification of PAN were originally designed to distinguish PAN from other types of vasculitides, but not to distinguish PAN from other diseases [4]. Furthermore, in recent years, some types of vasculitides (i.e., Takayasu arteritis) could be easily differentiated from PAN through imaging tests [11]. Accordingly, the specificity of the ACR criteria in recent clinical practice may not be as high as previously reported. On the other hand, our criteria were developed from a real-world cohort

Table 3 The seven-item criteria for a diagnosis of polyarteritis nodosa[a]

Item	Definition
Mononeuropathy multiplex	Mononeuropathy multiplex on neurologic examination or electrophysiologic study
Gastrointestinal involvement	Ischemic lesions of the gastrointestinal tract, or appendicitis or cholecystitis due to vasculitis. Results of imaging tests, such as contrast-enhanced CT, suggesting these findings can also be included
Absence of MPO-ANCA	Absence of MPO-ANCA, determined by local laboratory standards (i.e., ELISA). MPO-ANCA can be replaced with a "perinuclear" pattern on immunofluorescence staining where measurement of MPO-ANCA is unavailable
Urine protein < 2 +	Urine protein < 2 + on the urine dipstick test
Fever for 1 week or weight loss of ≥ 4 kg	Unexplained fever ≥ 38℃ for at least 7 days or weight loss ≥ 4 kg since onset of illness not due to other causes
Angiographic abnormality	Aneurysms, stenosis, or occlusions of the visceral arteries, not due to other causes. Angiogram can be replaced with contrast-enhanced CT or magnetic resonance angiography
Histologic evidence on biopsy	Granulocytes or mixed leukocyte infiltrates in an arterial wall of a medium or small artery

CT computed tomography, *ELISA* enzyme-linked immunosorbent assay, *HPF* high-power field, *MPO-ANCA* myeloperoxidase-anti-neutrophil cytoplasmic antibody, *RBC* red blood cell

[a]A cutoff value ≥ 4 points had a sensitivity of 92.3% and a specificity of 91.7%

of patients suspected of PAN, and our non-PAN population included both vasculitis and non-vasculitic conditions. The specificity of the ACR criteria of 79.2% in our study was not as high as that in the Diagnosis and Classification in Vasculitis Study (DCVAS) (92.5%) [6]. This suggests that our non-PAN population may be relatively difficult to differentiate from the PAN group compared with the non-PAN population of the DCVAS. The seven-item criteria for diagnosis of PAN yielded a higher specificity (91.7%) in such a population.

Several limitations of this study must be considered. First, the study was retrospective in nature and included a small sample size, leading to selection bias. Second, our small population did not allow use of multivariate analysis for developing the criteria. However, the seven-item criteria achieved the most favourable performance among the 18 candidate models. Finally, our provisional criteria should be evaluated for validation in a larger cohort suspected of PAN, as has been done with previous criteria for other rheumatic diseases [12, 13]. Despite these limitations, this study was the first attempt to develop diagnostic criteria for PAN in a real-world population with suspicion of PAN.

Conclusions

The provisional seven-item diagnostic criteria for PAN had a high sensitivity of 92.3% and specificity 91.7% and may be useful in the patient population where PAN is suspected in clinical settings.

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Author contributions Both the authors met the four criteria that ICMJE recommended: (1) substantial contributions to the conception or deign of the work; or the acquisition, analysis, or interpretation of data for the work AND (2) drafting the work or revising it critically for important intellectual content AND (3) final approval of the version to be published AND (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. We declare both the authors take full responsibility for all aspects of the study and the final manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical standards This study complied with the Declaration of Helsinki, and the institutional review boards of the Hiroshima City Hiroshima Citizens Hospital approved this study (approval number: 2019–157). The need to obtain informed consent from the patients was waived in accordance with the regulations for retrospective cohort studies. Information for patients regarding this study was provided on our hospital's website.

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