Arch Dermatol Res (2009) 301:117–121
DOI 10.1007/s00403-008-0898-2

REVIEW

Cutaneous polyarteritis nodosa: revisiting its definition and diagnostic criteria

Tomoyuki Nakamura · Nobuo Kanazawa · Takaharu Ikeda · Yuki Yamamoto · Kimimasa Nakabayashi · Shoichi Ozaki · Fukumi Furukawa

Received: 11 August 2008 / Accepted: 24 August 2008 / Published online: 19 September 2008

Abstract Polyarteritis nodosa (PN) is a classical collagen disease with poor prognosis that demonstrates systemic necrotizing vasculitis of small and medium-sized arteries. Cutaneous symptoms are observed in 25–60% of PN patients. On other hand, cutaneous polyarteritis nodosa (CPN) is designated for the cutaneous limited form of PN and demonstrates benign prognosis. However, there has been much debate on whether or not CPN can progress to PN. Although CPN lesions are fundamentally limited to skin, some CPN cases show extracutaneous symptoms such as peripheral neuropathy and myalgia. According to PN diagnostic criteria, which were established by the Ministry of Health, Labour and Welfare of Japan, a disease with both cutaneous and at least one extracutaneous symptom with appropriate histopathological findings can be diagnosed as PN. The same is true according to diagnostic criteria established by the American College of Rheumatology. In addition, there are no specific diagnostic criteria for CPN. In this study, CPN cases were retrospectively collected from multiple Japanese clinics, and analyzed for detailed clinical and histopathological manifestations, in order to redefine the clinical entity of CPN and to propose appropriate diagnostic criteria for CPN and PN. According to the CPN description in Rook's Textbook of Dermatology, we collected 22 cases with appropriate histopathological findings. Of the 22 cases, none progressed to PN or death during the follow-up period, 32% had peripheral neuropathy and 27% had myalgia. Regarding extracutaneous symptoms with CPN, 17 dermatological specialists in vasculitis sustained the opinion that CPN can be accompanied by peripheral neuropathy and myalgia but these symptoms are limited to the same area as skin lesions. Based on these results, we devised new drafts for CPN and PN diagnostic criteria. Our study shows the efficacy of these criteria and most dermatologists recognized that our new diagnostic criteria for CPN and PN are appropriate at the present time. In conclusion, this study suggests that CPN does not progress to PN, and introduces new drafts for CPN and PN diagnostic criteria.

Keywords Cutaneous polyarteritis nodosa · Clinical entity · Definition · Diagnostic criteria · Extracutaneous symptoms

T. Nakamura (✉) · N. Kanazawa · T. Ikeda · Y. Yamamoto · F. Furukawa
Department of Dermatology, School of Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-0012, Japan
e-mail: nkmr@wakayama-med.ac.jp

K. Nakabayashi
First Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

S. Ozaki
Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, Kanagawa, Japan

Introduction

Polyarteritis nodosa (PN) is a classical collagen disease with poor prognoses that shows systemic necrotizing vasculitis of small and medium-sized arteries. Cutaneous symptoms are observed in 25–60% of PN patients [5]. On other hand, cutaneous polyarteritis nodosa (CPN) is designated for the cutaneous limited form of PN. CPN has been described as a distinct clinical entity with benign and chronic courses without systemic involvement [2, 6–9, 15].

Table 1 Clinical features of 22 patients with cutaneous polyarteritis nodosa

Patient no.	Sex/age at onset (year)	Cutaneous manifestations	Localization	Extracutaneous manifestations	Follow-up (year)
1	F/56	●	●Lower leg	–	1
2	F/73	● ■	●■Lower leg	Peripheral neuropathy	2
3	F/37	●	●Lower leg	–	2
4	F/54	●	●Lower leg	–	1
5	M/54	● □	●□Lower leg	Fever, Myalgia, Arthralgia	1
6	F/55	■□	■□Lower leg	Peripheral neuropathy	2
7	M/51	●○	●Thigh, forearm ○instep	Myalgia	4
8	F/25	●○	●○lower leg	Arthralgia	1
9	F/21	○■□	○heel ■heel∼sole □instep	Peripheral neuropathy	3
10	F/34	● ■	●■lower leg, thigh	Myalgia	2
11	F/77	●○■	●■lower leg ○lower leg, thigh	–	1.5
12	M/63	○■	○lower leg, instep, back ■lower leg	Fever, Weight loss, Peripheral neuropathy, Myalgia	2.5
13	F/61	●○	●○lower leg	–	1
14	F/55	●○■	●○■lower leg, foot	Peripheral neuropathy	1
15	F/51	● ■□	●■□lower leg	–	1
16	F/22	●	●upper limb, lower limb	Fever, Myalgia	13
17	F/60	●○	●○lower leg	Fever	5
18	F/49	● ■	●■lower leg	–	9
19	F/53	●	●lower leg	–	1
20	F/17	●○■	●○■lower leg	Peripheral neuropathy	1
21	F/56	●○ □	●lower leg ○lower leg, forearm □lower leg	Arthralgia	12
22	F/35	●	●lower leg, foot, forearm, palm	Peripheral neuropathy, Myalgia, Arthralgia	1

● Subcutaneous nodules, ○ livedo, ■ purpura, □ ulcers

However, since it is impossible to distinguish cutaneous manifestations of PN from those of CPN, there has been much debate on whether or not CPN can progress to PN.

Although CPN lesions are fundamentally limited to skin, some CPN cases reportedly show extracutaneous symptoms such as peripheral neuropathy, myalgia, and arthralgia. In these cases, CPN diagnoses were made because extracutaneous symptoms were limited to the same area as skin lesions and were considered secondary to skin damage. On the contrary, another school of thought is that a disease is diagnosed as PN when extracutaneous symptoms accompany skin lesions [3]. PN diagnostic criteria, which were established by the Ministry of Health, Labour and Welfare (HLW) of Japan, do not mention CPN and seem to be based on the latter opinion. According to the aforementioned criteria, a disease with both cutaneous and at least one extracutaneous symptom with appropriate histopathological findings can be diagnosed as PN, even if all the symptoms are concentrated to limited areas. The same is true according to diagnostic criteria established by the American College of Rheumatology [11]. In addition, there are no specific diagnostic criteria for CPN.

Therefore, in this study, CPN cases, as assessed by clinical specialists were retrospectively collected from multiple Japanese clinics, and analyzed for detailed clinical and histopathological manifestations, in order to redefine the clinical entity of CPN and to propose appropriate diagnostic criteria for CPN and PN.

Methods

According to the CPN description in Rook's Textbook of Dermatology [1], we collected 22 cases of CPN seen in 6 Japanese dermatological clinics between 1996 and 2007, including 5 cases in our clinic. All the cases were reviewed retrospectively regarding the age, sex, cutaneous, and histopathological manifestations, skin lesions, laboratory findings, and follow-up period.

In addition, we sent series of questionnaires regarding extracutaneous symptoms with CPN to 17 dermatological specialists in vasculitis.

Based on these results, we devised a new draft of diagnostic criteria for CPN, and amended the present diagnostic criteria for PN to exclude CPN. Furthermore, we sent series of questionnaires regarding our new drafts to the 17 dermatological specialists in vasculitis.

Results

Twenty-two cases of CPN were collected from six clinics in Japan, including five from our clinic. The aforementioned cases were comprised of 19 female and 3 male patients. Detailed information regarding these cases is summarized in Tables 1 and 2. The average age at onset for female patients was 46.6 years (range 17–77) and 56.0 years (range 51–63) for male patients. The average follow-up period was 3.1 years (range 1–13). Notably, although six patients were followed for more than 3 years, none of the cases progressed to PN or death during the follow-up period.

Although C-reactive protein elevations were found in 14 patients, marked elevations above 3.0 mg/dl were found in only five patients (patient 12, 13, 14, 17 and 21). Positive antinuclear antibody tests were found in three patients with low titers (patient 5, 18 and 20). Hepatitis B surface antigens were tested in 13 of the 22 patients, and were always negative. None of the blood tests for anti-neutrophil cytoplasmic antibodies (ANCA) were positive. Visceral angiography was performed in only four patients (patient 10, 11, 12 and 17), and there was no evidence of aneurysms in any patient. For treatment, 68% of patients received systemic corticosteroids (10–40 mg of oral prednisolone daily).

On skin biopsies, all patients showed fibrinoid necrotizing vasculitis in small and medium-sized arteries within deep dermal or subcutaneous tissues without visceral involvement. Of these 22 patients, 86% had subcutaneous nodules, which represented the most frequent cutaneous manifestation, while 64% had extracutaneous manifestations such as peripheral neuropathy, myalgia, arthralgia, fever, and weight loss without visceral involvement. Especially, 32% had peripheral neuropathy and 27% had myalgia. Regarding the peripheral neuropathy and myalgia accompanied with CPN, all 17 dermatologists specializing in vasculitis, answered questionnaires to sustain the opinion that CPN can be accompanied with peripheral neuropathy and myalgia but these symptoms are limited to the same area as skin lesions.

Table 2 Clinical manifestations of 22 patients with cutaneous polyarteritis nodosa

1. Cutaneous manifestations	
Subcutaneous nodules	86%
Livedo	45%
Purpura	45%
Ulcers	23%
2. Localization of each cutaneous manifestations	
Subcutaneous nodules	
Lower limb	100%
Upper limb	16%
Livedo	
Lower limb	80%
Forearm	10%
Back	10%
Purpura	
Lower limb	100%
Ulcers	
Lower limb	100%
3. Extracutaneous manifestations	
Peripheral neuropathy	32%
Myalgia	27%
Arthralgia	18%
Fever	18%
Weight loss	5%
Any	64%

Based on these results, a new draft for CPN diagnostic criteria was devised as shown in Table 3. Histopathological findings were indispensable to exclude other cutaneous vasculopathies. Regarding PN diagnostic criteria, those established by the Ministry of HLW of Japan were amended by adding differential CPN diagnosis. The above-mentioned 22 patients were all appropriately diagnosed as CPN using these criteria. Of the 17 dermatological specialists in vasculitis, 88% answered that our new draft of diagnostic criteria for CPN are appropriate, and 82% answered that the draft for PN is appropriate at the present time.

Discussion

CPN was first described by Lindberg [12] in 1931 as necrotizing vasculitis localized skin lesions which have the same clinical manifestations and microscopic findings as PN, but

Table 3 A new draft of diagnostic criteria for cutaneous polyarteritis nodosa

1. Cutaneous manifestations
Subcutaneous nodules, Livedo, Purpura, Ulcers
2. Histopathological findings
Fibrinoid necrotizing vasculitis of small and medium-sized arteries
3. Exclusion manifestations
(1) Fever (≧38°C, ≧2 weeks), Weight loss (6 kg or more in 6 months)
(2) Hypertension
(3) Rapidly progressive renal failure, Renal infarction
(4) Cerebral hemorrhage, Cerebral infarction
(5) Myocardial infarction, Ischemic heart disease, Pericarditis, Heart failure
(6) Pleuritis
(7) Intestinal hemorrhage, Intestinal infarction
(8) Peripheral neuropathy out of the affected skin lesion
(9) Arthralgia (arthritis) or myalgia (myositis) out of the skin lesion
(10) Abnormal arteriography (multiple microaneurysm, stenosis and obliteration)
4. Decision
Both cutaneous manifestations and histopathological findings without exclusion manifestations

are characterized by a chronic, benign course without systemic involvement [2, 6–9, 15]. Daoud et al., [6] reviewed 79 cases of CPN, and reported that none progressed to PN. Our study also showed that CPN does not progress to PN. Recently, Kawakami et al., [10] reported anti-phosphatidylserine-prothrombin complex (anti-PS/PT) antibodies and/or lupus anticoagulants (LAC) were detected in all CPN patients, but not in controls. These studies strongly suggest a distinct clinical entity for CPN.

On other hand, although rare, some cases represent a form of PN, which initially showed mere skin lesions and progressed to the systemic form after a long period of follow-up [4, 13, 14]. Therefore, the careful long-term follow-up of a patient with CPN is considered necessary. A potential limitation to our study is that the follow-up period of patients may not be long enough to decide whether the disease is really CPN or not. Although inflammatory changes of systemic and cutaneous lesions seem more severe in such PN cases, compared with those of CPN, it is impossible to distinguish them at the moment. Indeed, it is very important but it is a difficult challenge for a clinician, to give a diagnosis and explain a prognosis to a patient at an early stage of the disease. A prospective study would be necessary to evaluate the possibility that anti-PS/PT and/or LAC would be an appropriate diagnostic marker for CPN. At this point, problems associated with distinguishing CPN from PN are similar to those distinguishing discoid lupus erythematosus from systemic lupus erythematosus, and those distinguishing morphea from systemic sclerosis.

Another problem with distinguishing CPN from PN is how extracutaneous symptoms are estimated, such as peripheral neuropathy, myalgia, and arthralgia. In this study, 64% of CPN patients had extracutaneous symptoms without visceral involvement and all the dermatologists, specialized in vasculitis, agreed with the opinion that CPN can be accompanied with peripheral neuropathy and myalgia, when these symptoms are limited to the same area as skin lesions. In contrast, PN often has peripheral neuropathy and myalgia in areas unrelated to skin lesions [3].

To reflect these facts, a new draft of diagnostic criteria for CPN was devised and the present diagnostic criteria for PN were amended to exclude CPN (Table 3). Our study shows the efficacy of these criteria and most dermatologists recognized that our new drafts are appropriate at the present time.

In conclusion, this study suggests that CPN does not progress to PN, and introduces new drafts for CPN and PN diagnostic criteria.

We investigated this study as a task of the Ministry of HLW of Japan.

Acknowledgments We are grateful to the following dermatologists for their cooperation in providing information on CPN patients and providing answer to our questionnaires; Hiroyuki Okamoto, MD (Kansai Medical University), Atsushi Utani, MD (Kyoto University), Yayoi Nagai, MD (Gunma University), Osamu Yamasaki, MD (Okayama University), Taisuke Itoh, MD (Hamamatsu University School of Medicine), Takatoshi Shimauchi, MD (University of Occupational and Environmental Health), Toshiyuki Yamamoto, MD*, Yumiko Furuhata, MD (Tokyo Medical University), Ko-Ron Chen, MD (Saiseikai Central Hospital), Tamihiro Kawakami, MD (St. Marianna University School of Medicine), Naoko Ishiguro, MD (Tokyo Women's Medical University), Setsuya Aiba, MD (Tohoku University), Kensei Katsuoka, MD (Kitasato University), Mikio Masuzawa, MD (Kitasato University), Seiji Kawana, MD (Nippon Medical School), Shinichi Sato, MD (Nagasaki University), Eishin Morita, MD (Shimane University), Seiichi Izaki, MD (Saitama Medical University). * Currently at the Department of Fukushima Medical University.

Conflict of interest statement The authors have no potential conflict of interest.

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