

Cutaneous Polyarteritis Nodosa: An Update

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Cutaneous symptoms are observed in 25%–60% of polyarteritis nodosa (PN) patients. On the 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, 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 American College of Rheumatology (ACR). 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, one of global standard textbooks, 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. (*English Translation of J Jpn Coll Angiol 2009; 49: 87-91.)

Keywords: cutaneous polyarteritis nodosa, clinical entity, definition, diagnostic criteria, extracutaneous symptoms

INTRODUCTION

Skin lesions are observed in 25%–60% of patients with polyarteritis nodosa (PN)^{1,2)} and include subcutane-

ous nodules, livedo reticularis, ulcers, and gangrene. PN is systemic vasculitis, and discussion has been made on the association between skin and systemic lesions, i.e., whether a pathological condition in which vasculitis is limited to the skin is present or not, and, if present, how it is diagnosed and what its prognosis is. When other collagen vascular diseases are taken as examples, discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE) or localized scleroderma and systemic scleroderma are two distinct clinical entities, but the former sometimes shows progression to the latter. It is a question whether PN in which vasculitis is limited to the skin and PN can be similarly regarded as two distinct clinical entities. In this study, based on our clinical data^{3–5)} (Table 1), we

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Table 1 Clinical features of 22 patients with cutaneous polyarteritis nodosa

Patient No.	Sex/Age at onset (yr)	Cutaneous manifestations	Localization	Extracutaneous manifestations	Follow-up (yr)
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

focused on the independence of cutaneous PN (CPN).

WHAT IS CPN?

In 1931, Lindberg described cases of necrotizing vasculitis, which was limited to the skin but could not be histopathologically distinguished from PN, as cases

of CPN. The characteristics of CPN were: (1) findings of vasculitis limited to the skin, (2) histopathological findings of skin biopsy similar to those of PN (necrotizing vasculitis in small arteries in the lower dermal layer or subcutaneous fat tissue), and (3) absence of internal organ lesions.

Concerning the pathogenesis of CPN, type III allergic



Fig. 1 Subcutaneous nodules.



Fig. 2 Ulcer.

reactions mediated by immune complexes are assumed. However, this theory was formed by analogical inference drawn from the pathology of systemic PN. As described below, the background for the pathogenesis of CPN may differ from that for PN. Therefore, the pathogenesis of CPN should be evaluated in terms of not only allergic reactions but also circulatory or vascular impairment. Although the cause of CPN is unknown, the involvement of streptococcal infection and hepatitis virus infection has been suggested. However, at least in Japan, there have been few results suggesting an association with HBV or HCV infection.⁶⁾

In the dermatological field, CPN shows a prolonged course with repeated skin manifestations, but is generally considered to be distinct from PN due to its favorable prognosis. However in other departments such as the Department of Internal Medicine, the characteristics of CPN are not adequately understood. This is because of the lack of diagnostic criteria or evidence and inconsistent interpretation of neurological findings.

CLINICAL SIGNS AND SYMPTOMS OF CPN

CPN frequently affects females aged ≥ 40 years, with numbers of patients peaking at 50–59 years of age. PN more frequently affects females (male: female ratio = 2: 3), showing a peak number of patients at 60–80 years of age.⁷⁾ The skin manifestations of CPN as well as PN include nodules (subcutaneous nodules) (**Fig. 1**), livedo reticularis, ulcers (**Fig. 2**), and gangrene. Purpura, papules, atrophie blanche, and edema have also been reported. The incidences and sites of these lesions are shown in **Table 2** (modified based on Ishiguro's table⁶⁾). As shown in this table, the incidences of nodules (80%–100%) and livedo reticularis (45%–80%) are high, and the legs are the most frequently affected.

The nodules frequently have a diameter ≤ 1 cm and are multiple, red-dark reddish-purple, and accompanied by spontaneous pain and tenderness. Ulcers develop in nodules and livedo lesions. Since ulcers and gangrene are frequent complications, treatment is often difficult.

Table 2 Skin lesion, frequency, and sites of CPN

	Borrier ^{*1)} (15 cases)	Diaz-Perez ^{*2)} (23)	Daoud ^{*3)} (79)	Chen ^{*4)} (20)	Nakamura & Furukawa ⁵⁾ (22)
<skin lesion>					
nodule	100%	82.6%	79.7%	90%	86.3%
livedo	66.7	78.3	55.7	80	45.5
ulcer	20	39.1	49.4	35	22.7
gangrene	13.3			15	n.d.
<site>					
leg	100%	95.7%	97.5%		100%
arm	33.3	60.9	32.9		18.2
head, neck	26.7	39.1			0
trunk	20	34.8	7.6		4.5
buttock		21.7			0

*1) Borrie P: Br J Dermatol, 1972, 87: 87–95.

*2) Diaz-Perez JL, Winkelmann RK: Arch Dermatol, 1974, 110: 407–414.

*3) Daoud MS, Hutton KP, Gibson LE: Br J Dermatol, 1997, 136: 706–713.

*4) Chen KR: J Dermatol, 1989, 16: 429–442.

As extracutaneous manifestations, fever, arthralgia, peripheral neuropathy, and myositis are observed, and the incidences of peripheral neuropathy and myositis are both 22%–66%. Our investigation showed neurological and muscular manifestations in 32 and 27%, respectively (**Table 1**).

In CPN, unlike PN, laboratory examination shows only a few abnormalities such as increases in inflammatory markers and a positive antinuclear antibody titer, but these abnormalities are mild.

PATHOLOGICAL FINDINGS

In medium and small-sized arteries, necrotizing vasculitis involving all layers of the vascular wall accompanied by fibrinoid degeneration is observed. As the histological stage classification of PN, Arkin's classification⁸⁾ is widely used in the world. Stages I (degenerative stage) and II (inflammatory stage) are vascular inflammation stages in which edema and/or fibrinoid degeneration of the media and intima occur, and the infiltration of inflammatory cells, mainly neutrophils, eosinophils, lymphocytes, and plasma cells, is observed. Fibrinoid degeneration involves all layers of the vascular wall, and the internal elastic lamina is disrupted. Skin tissue basically shows similar findings, i.e., necrotizing vasculitis in small arteries from the dermal-subcutaneous border to subcutaneous tissue (**Figs. 3 and 4**). In stages III (granulation tissue stage)

and IV (scar tissue stage), histiocyte and fibroblast invasion from the adventitia occurs, inducing stenosis of the vascular lumen due to new granulation tissue formation and intimal proliferation, and resulting in obstruction due to fibrotic tissue and aneurysm formation. Chin proposed a classification of CPN into 3 stages (acute, repair, and scar stages) because of differences in the target vessel size.⁹⁾ The histological findings in Arkin's stages I-IV are mixed in the same patients.

INDEPENDENCE OF DISEASE

Unlike PN, CPN relatively frequently develops in young females. Inflammatory reactions, even if present, are mild, and the prognosis is favorable. Daoud et al.¹⁰⁾ evaluated 79 patients with CPN, but did not observe progression to PN. In our study, none of the patients died or showed progression to PN. Thus, CPN and PN can be considered to be two independent diseases. However, since rare cases showing progression to PN during long-term follow up have also been reported,¹¹⁾ careful observation of the course is necessary. Recently, Kawakami et al. reported the presence of an antibody against the CPN-specific phosphatidylserine-prothrombin complex.¹²⁾ Based on these reports, it may be rational to regard CPN as an independent disease entity.

Here, the problem is the presence of associated extracutaneous symptoms such as mild peripheral neuropathy symp-

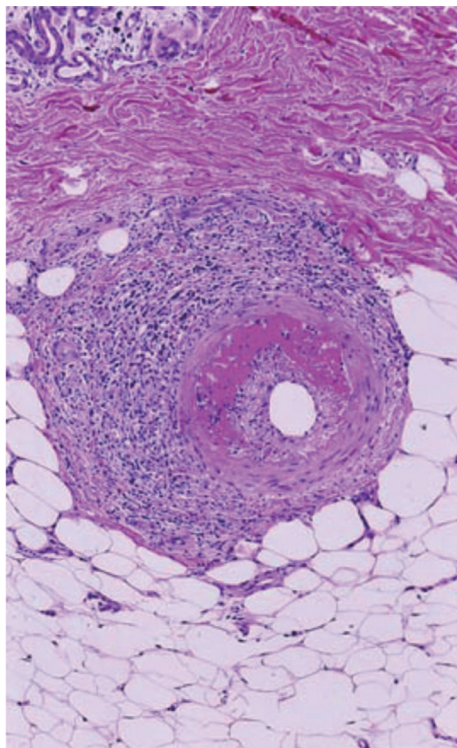


Fig. 3 Histology of CPN (HE).
(Prof. Ishikawa, Gunma University)

toms, arthralgia, and myalgia. It may be straightforward to define cases without associated extracutaneous symptoms as CPN, but there are many opinions that this definition is not practical in a clinical setting. In this study, peripheral neuropathy symptoms were present in about 30% of the patients and certain associated extracutaneous symptoms in more than 50%. The interpretation of these associated symptoms is a problem. According to the diagnostic criteria proposed by the Ministry of Health, Labour and Welfare or the American College of Rheumatology (ACR), CPN with associated extracutaneous symptoms is diagnosed as PN. We performed a questionnaire survey in major dermatological departments providing treatment for vasculitis throughout Japan (a total of 17 subjects including 10 members of the Committee of the Japan Dermatological Association for the Establishment of Guidelines for Vasculitis and Vasculopathy), and all subjects supported the opinion that a diagnosis of CPN is made when associated symptoms (peripheral nerve symptoms and/or muscular symptoms) are localized in eruption portions even if they are due to vasculitis. (The other choices were: a) A diagnosis of PN is made when associated symptoms are due to vasculitis, and b) others).

Therefore, we proposed draft diagnostic criteria for

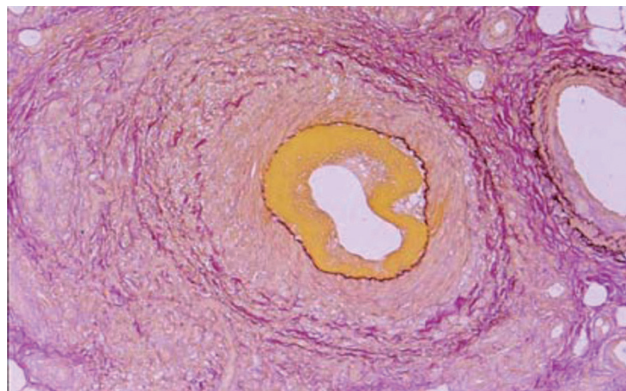


Fig. 4 Histology of CPN (elastic fiber staining).
(Prof. Ishikawa, Gunma University)

CPN, as shown in **Table 3**.⁵⁾ In the diagnostic criteria for PN, differentiation from CPN was included as follows: VI. Differential diagnosis: (1) Wegener's granulomatosis, (2) allergic granulomatous angiitis, (3) microscopic PN, (4) vasculitis in Kawasaki disease, and (5) CPN.

Since progression to PN occurs extremely rarely during long-term follow-up, there is a criticism that the term "CPN" is misleading. However, it is important to make a diagnosis when CPN is detected, and explain its prognosis and treatment to patients. CPN and PN can be considered to be similar to DLE and SLE or morphea and systemic scleroderma.

POINTS FOR DIAGNOSIS

Due to small arteries being damaged in both PN and CPN, red-dark red, painful, subcutaneous nodules and livedo reticularis are particularly important as cutaneous manifestations, which are observed mainly on the legs. Differentiation of between PN and CPN based on skin eruptions is difficult, but there are various types of eruption including gangrene and bloody bullae in PN, while the internal elastic lamina is often histologically maintained in CPN. In addition, in PN, peripheral neuropathy and muscular symptoms are also observed in areas other than those with eruptions.⁹⁾

Even when CPN is suspected based on skin lesions and pathological findings, the possibility that they are parts of PN manifestations should always be considered during consultation and close examination. In addition, diseases requiring differentiation shown in **Table 3** and other types of vasculitis (such as cutaneous allergic vasculitis and thrombophlebitis) and collagen vascular diseases (such as SLE and rheumatoid arthritis) should be excluded. Skin

Table 3 A new draft of diagnostic criteria for cutaneous polyarteritis nodosa⁵⁾

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 ($\geq 38^{\circ}\text{C}$, ≥ 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

biopsy can be readily performed, and is extremely useful for a definite diagnosis. However, since damaged blood vessels are present from the dermal lower layer to subcutaneous fat tissue, unless markedly inflammatory lesions are collected down to the subcutaneous tissue, findings cannot be obtained. For ulcer lesions, the area central to the ulcer should be biopsied. When lesions cannot be confirmed, serial sections are prepared, or re-biopsy should also be considered. In the scar tissue stage, inflammatory cell infiltration is mild, and diagnosis is difficult using H.E. staining alone; elastica van Gieson staining that can confirm the internal elastic lamina is useful.

TREATMENT

Patients with mild CPN often show improvement after rest of the legs and the administration of nonsteroidal anti-inflammatory drugs (NSAIDs). In patients who do not respond to these methods and those with severe CPN, systemic steroid administration at a moderate dose is used in combination with these methods. Although the effectiveness of NSAIDs or systemic steroid administration has not been adequately evaluated by randomized or non-randomized controlled trials, their administration can be considered. There have been retrospective case series studies on the effectiveness of systemic steroid administration, and many of them showed patients who responded to this administration. Systemic immunosup-

pressant administration can be considered in patients with intractable CPN who do not respond to other treatment methods including steroid administration, but adequate attention to the possible development of adverse effects is necessary.⁶⁾

Treatment methods that improve circulation (anticoagulants, thrombolytic agents, anti-platelet drugs, vasodilators) are also attempted, and can be actively considered in patients showing markedly impaired circulation due to ulcers or gangrene. In treatment-resistant cases, colchicine and dapsone are also used, but their definite effectiveness has not been reported.

As a cause, the involvement of streptococcal infection is strongly considered. In patients with CPN showing repeated recurrence, the prophylactic administration of penicillin antibiotics for infection lesions can be considered, but its adequate evaluation has not been performed.

There is no specific treatment using drugs for external use. The selection of drugs for external use based on the wound healing theory is important. Disinfectants such as povidone iodine occasionally cause aggravation of ulcers due to their cytotoxic effects. Local washing with physiological saline is often adequate.

PROGNOSIS

Despite repeated recurrence during a long period, the prognosis of CPN is favorable. However, since progres-

sion to PN is considered to occur in some patients, careful follow-up is necessary. In particular, attention should be paid to patients with repeated skin ulcers/gangrene, marked peripheral neuropathy, a positive antinuclear antibody titer or rheumatoid factor level, immune abnormalities such as a marked increase in immunoglobulin, an increase in the erythrocyte sedimentation rate, and marked inflammatory reactions such as an increase in the leukocyte count. Ishiguro analyzed the pathology of CPN in detail based on outcomes, and proposed a smoldering type as initial CPN, which is worth evaluation.¹³⁾

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