別紙４

研究成果の刊行に関する一覧表

雑誌

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Ⅴ　研究成果の刊行物・別冊

Mod Rheumatol (2009) 19:80–83
DOI 10.1007/s10165-008-0119-z

CASE REPORT

Treatment of refractory retrobulbar granuloma with rituximab in a patient with ANCA-negative Wegener's granulomatosis: a case report

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Received: 23 May 2008 / Accepted: 29 July 2008 / Published online: 18 September 2008

Abstract Retrobulbar granuloma is one of the serious complications in Wegener's granulomatosis and often shows resistance to conventional therapy during long-term treatment. The outcome of this complication includes visual loss, orbital and facial deformity, fistula formation, as well as infection. There has been increasing evidence that shows the efficacy of rituximab, a chimeric anti-B cell mAb, for the treatment of autoimmune diseases including Wegener's granulomatosis. We present a 22-year-old Japanese woman who was diagnosed with Wegener's granulomatosis complicated by refractory retrobulbar granuloma. She was admitted to our hospital with pain of the right eye and right proptosis during treatment with monthly IVCY for Wegener's granulomatosis. We diagnosed refractory retrobulbar granuloma by computed tomography (CT) scan and biopsy. She showed a refractory growth of retrobulbar granuloma in spite of negative ANCA. She was also complicated with pulmonary granulomatous lesions in bilateral apices. After approval by an institutional ethical committee and informed consent of this patient, rituximab 375 mg/m^2 was intravenously administered weekly four times. Concomitant prednisolone 0.5 mg/kg was also administered for 2 weeks and gradually tapered. Treatment of rituximab resulted in prompt relief of symptoms in this case and the reduction of the granuloma. BVAS score also improved from 6 to 0 at 3 months and was kept in remission for 12 months. Circulating CD19-positive cells were kept less than 0.1% during the follow-up. There were no serious adverse events. This case suggests that rituximab is effective for refractory retrobulbar granuloma complicated in Wegener's granulomatosis even when ANCA titers are negative.

Keywords Rituximab · Wegener's granulomatosis · Retrobulbar granuloma · PR3 ANCA-negative

Introduction

Wegener's granulomatosis (WG) is a systemic vasculitis characterized by necrotizing granulomatous inflammation and vasculitis of the upper and lower respiratory tracts and focal necrotizing glomerulonephritis. Retrobulbar granuloma is one of the serious complications and often shows resistance to conventional therapy during long-term treatment. The outcome of this complication includes visual loss, orbital and facial deformity, fistula formation, and infection. There has been increasing evidence that shows the efficacy of rituximab, a chimeric anti-CD20 mAb, for the treatment of ANCA-positive Wegener's granulomatosis. We report here a case with WG and cyclophosphamide-resistant retrobulbar granuloma that showed rapid improvement after the administration of rituximab in the absence of circulating ANCA.

Case

A 21-year-old female presented with right ophthalmalgia and right proptosis. She had been well until January, 2005, when she developed a nasal obstruction, dacryorrhea, and blepharedema. Computed tomography (CT) scan revealed an intranasal mass. Nasal biopsy showed a granulomatous

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lesion. She further developed persistent cough with infiltration of both upper lung fields, and a mass lesion extended to both orbits in March. She was diagnosed with a limited form of WG based on the upper respiratory tract symptoms with intranasal granuloma (E), Pulmonary infiltration (L), and positive PR3-ANCA. She was treated with PSL 30 mg/day + intravenous pulses of cyclophosphamide (IVCY) (0.5 g/m^2), resulting in a remission. Monthly IVCY was performed for a total of seven times. Two weeks after the 7th-IVCY the patient complained of painful swelling of the lateral side of the right upper eye lid and antibiotics-resistant coughing in January, 2006. Brain MRI showed an increased volume of retrobulbar mass lesion, and she was admitted to the hospital in March of 2006.

Upon admission, the patient had episcleritis and proptosis in the right eye, with intact ocular movement and vision. She had right dominant hearing loss. A urine test revealed negative for blood and protein. Further blood tests revealed a leukocytosis of 10,500/μl, slightly elevated C-reactive protein (CRP) of 0.81 mg/dl, erythrocyte sedimentation rate of 23 mm/h and LDH levels of 340 IU/l. However, her PR3-ANCA was negative. CT scan revealed a granuloma in right orbita and the right lung (Fig. 1a, b). Because she showed a relapse during the seven times course of IVCY, we evaluated that retrobulbar and pulmonary granulomatous lesions were cyclophosphamide-resistant.

After approval of institutional ethical committee and informed consent of this patient, rituximab was introduced. Four infusions (375 mg/m^2 each) were given at weekly intervals. Prednisolone 30 mg daily was continued. After the second infusion of rituximab, the symptom of her cough and ophthalmalgia was improved. Her ANCA titer stayed negative and circulating CD19-positive B cells disappeared. Reevaluation with CT scan 3 months after treatment showed a reduction in the size of retrobulbar granuloma and disappearance of lung cavity (Figs. 1c, d, 2).

Discussion

Retrobulbar granuloma is one of the serious complications in Wegener's granulomatosis and often shows resistance to conventional therapy during long-term treatment. The outcome of this complication includes visual loss, orbital and facial deformity, fistula formation, and infection. Until recently, such patients had received surgical resection or ethanol injection.

There has been increasing evidence that shows the efficacy of rituximab, a chimeric anti-CD20 mAb, for the treatment of Wegener's granulomatosis [1–5]. Eleven cases that were treated with four weekly infusions of rituximab 375 mg/m^2, the same protocol as the present cases, showed marked improvement resulting in remission [3]. This response was associated with elimination of circulating B cells, and a decrease in ANCA titers. Remission was maintained during the period in which B cells remained absent. In another study, ten patients (seven with renal involvement) also underwent remission after treatment with rituximab and prednisone [4].

On the other hand, eight patients (five with retrobulbar and one with pulmonary/sinus granuloma, and two with

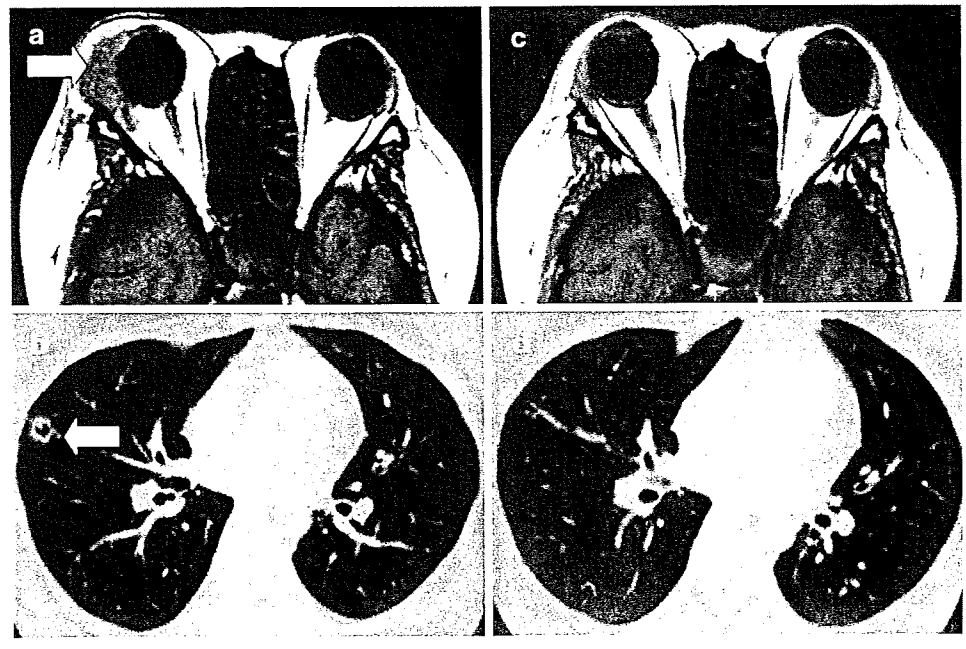

Fig. 1 Orbital and pulmonary granulomatous lesion before and 3 months after rituximab treatment. *Upper image* (**a**, **c**), orbit MRI (T1W1): Retrobulbar granuloma (*right arrow*) improvement tendency was accepted after rituximab treatment for 3 months. *Lower image* (**b**, **d**), chest CT: elimination of a cavernous lesion (*left arrow*) was accepted after a rituximab treatment for 3 months

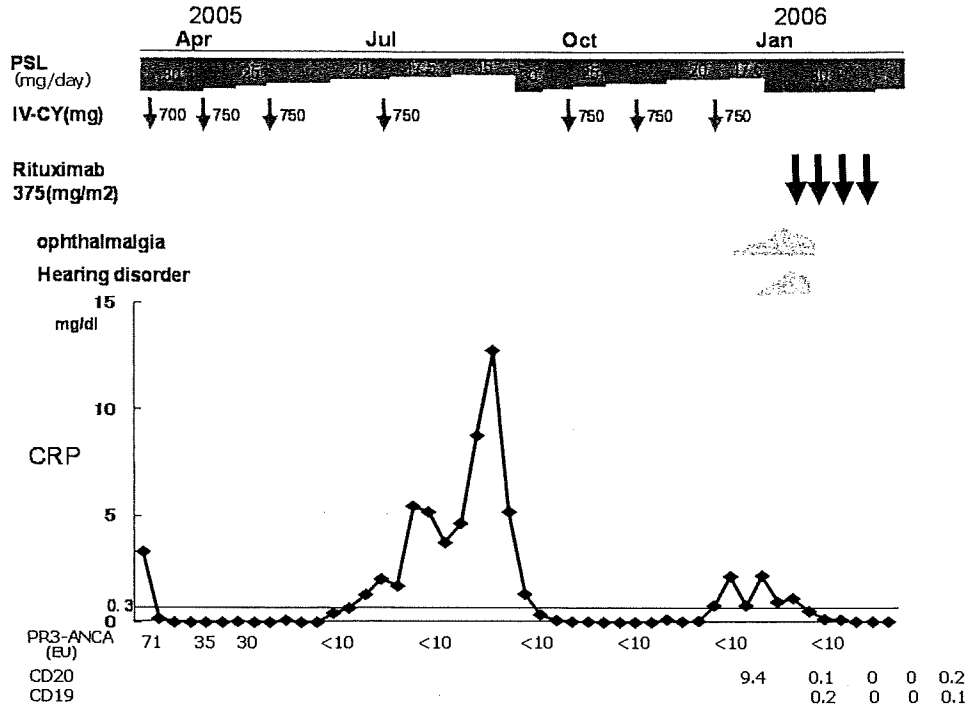

Fig. 2 Clinical course of this case

subglottic stenosis) who had not responded to conventional immunosuppression (PSL with CYC, MTX, leflunomide or MMF) and anti-TNFa antibody therapy were treated with infusion of rituximab every 4 weeks in combination with the standard treatment. Improvement in disease manifestations was noted in some, but in none of the patients with retrobulbar disease [6]. These results suggest that weekly administration is better than that administered, every 4 weeks.

There are two case reports suggesting that rituximab may be effective in treating Japanese patients with Wegener's granulomatosis [7, 8]. Similar to our case, both cases were women and both had a retrobulbar granuloma refractory to IVCY therapy. On the other hand, the previous two cases were ANCA-positive and were treated with steroid pulse therapy and rituximab. Our case report further supports the clinical efficacy of rituximab for Japanese patients with refractory retrobulbar granuloma complicated in Wegener's granulomatosis.

Although the mechanism of how rituximab works for the treatment of Wegener's granulomatosis is still controversial, the elimination of circulating B cells seems necessary for clinical improvement.

B-cell pathogenesis in autoimmune diseases has been historically attributed to autoantibodies that, in either soluble or IC forms, are thought to initiate local inflammatory cascades. The existence of long-lived autoimmune plasma cells has been demonstrated in murine models of SLE and suggested in humans. Although long- and short-lived terminally differentiated plasma cells down-regulate surface expression of CD20, and hence would not be depleted by anti-CD20 therapies, very little is known about their immediate precursors in autoimmune diseases. The minimal decreases observed in total serum Ig and more drastic reductions in autoantibody levels following rituximab treatment suggest either different precursor sensitivities to depletion or, alternatively, that autoantibody-producing plasma cells are enriched in shorter-lived subsets.

The present case responded to rituximab even though she was negative for ANCA before the treatment with rituximab. Although the serum of this case showed negative ANCA in a conventional ELISA system, there might be a possibility that she had small amount of ANCA less than the minimum sensitivity of the ELISA kit. Another explanation will be needed such as ANCA-independent B-cell contribution to the pathogenesis of Wegener's granulomatosis.

The contributions of antibody-independent mechanisms to B-cell function is illustrated in MLR/lpr mice made deficient in their ability to secrete Ig but with intact membrane Ig B cells and B cell effector functions—mIgM MRL/lpr [9]. Despite the absence of secreted Ig and anti-ds DNA antibodies, these mice still develop interstitial nephritis, vasculitis, and less, but still significant, glomerulonephritis and mortality when compared with secretory sufficient MLR/lpr. In contrast, Jh knockout MLR/lpr mice rendered completely B-cell-deficient exhibit minimal disease and mortality [10]. Hence, effector B cell functions, independent of secreted antibody, are also of paramount importance in disease development. A favored hypothesis

to explain these antibody-independent effects is the ability of B cells to present antigen to T cells as part of the pathogenic process.

Conclusions

This pilot study suggests that rituximab is effective for the refractory retrobulbar granuloma complicated in Wegener's granulomatosis even when ANCA titers are negative. Further prospective studies are needed to evaluate the efficacy and safety of rituximab therapy.

Conflict of interest statement All of the authors confirmed no conflict of interest with regard to this work.

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

REVIEW

Cutaneous polyarteritis nodosa: revisiting its definition and diagnostic criteria

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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

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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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臨床リウマチ，21： 85～90，2009

筋に特徴的な造影MRI所見を呈した皮膚型結節性多発動脈炎の一例

Key words: polyarteritis nodosa,
cutaneuos polyarteritis nodosa,
vasculitis,
magnetic resonance imaging,
diagnosis

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はじめに

皮膚型結節性多発動脈炎（cutaneous polyarteritis nodosa；CPAN）は，1931年にLindbergによりはじめて報告され，組織学的に典型的な結節性多発動脈炎（polyarteritis nodosa；PAN）の像を呈するが，病変は皮膚に限局し内臓病変を認めない疾患とされる[8]．また，PANは臓器障害のため時に致死的な経過となるが，CPANは慢性再発性であっても予後は良好とされる．

血管炎患者において筋痛は発熱，関節痛，食思不振などとともに主要な臨床症状の一つである．しかし，筋痛の病態を臨床検査で把握することはしばしば困難で，生検を施行しても十分な情報を得られないこともある．今回我々は，筋痛の検査にてガドリニウム造影MRIを施行し，筋に血管炎に伴う炎症所見を明瞭に確認できたCPANの症例を経験したので報告する．

症　例

患者：34歳　男性
主訴：左上肢の筋痛
既往歴：特になし
喫煙歴：喫煙習慣なし
飲酒歴：機会飲酒程度
家族歴：妹が拡張型心筋症
現病歴：15才頃より毛嚢炎，口内炎を繰り返していた．平成15年頃より下腿に紅斑が出現した．平成17年11月21日，当院皮膚科を初診し，浸潤をふれる紅斑，網状皮斑，関節痛よりBehcet病，血管炎を疑われた．11月24日，右下腿・左足背の皮疹より皮膚生検を施行し，壊死性血管炎を認めCPANと診断された（図1）．その後，塩酸サルポグレラート300 mg/日，リポプロスタグランジンE_1点滴（1回／2週，外来毎）の治療を開始された．

平成18年10月10日，口内炎，毛嚢炎，紅斑が増悪．Prednisolone（PSL）15 mg/日を開始された．以後症状に合わせて，PSLは適時増減（5

A case of cutaneous polyarteritis nodosa presenting with characteristic muscle Gadolinium —enhanced MRI findings.

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（2008．9．3 受付，2008.12．2 受理）

～15 mg/日）された．

平成19年12月2日，右大腿に疼痛が出現し歩行も困難となったため，12月3日に来院した．超音波検査にて右大伏在静脈に血栓を認め，深部静脈血栓症と診断され入院．ワーファリンによる抗凝固療法にて軽快し，12月10日に退院となった．

しかし，退院後もCRP 2 mg/dl前後と炎症反応が持続したため，平成20年1月7日当科に紹介受診．CPANの活動性が高いと考えPSLに加えてmethotrexate（MTX）を開始した．その後，PSLは漸減，MTXは漸増し，3月10日の時点でPSL 10 mg/日及びMTX 10 mg/週となった．3月上旬より，左上肢に筋痛が出現．

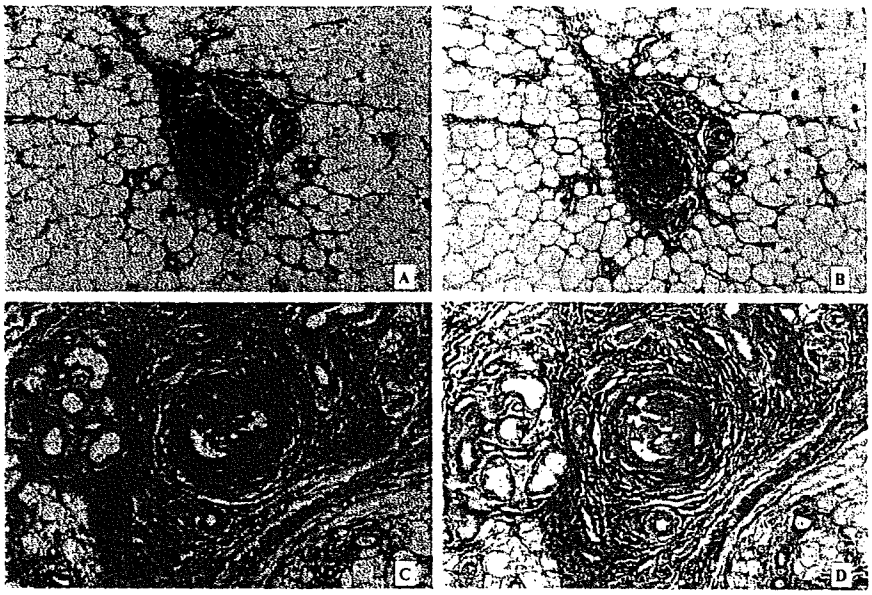

図1　皮膚生検（平成17年11月）
A：HE染色100倍，B：EVG染色100倍，C：HE染色200倍，D：EVG染色200倍
AおよびB：中膜，外膜に炎症細胞浸潤を認めた．また，血管内腔は炎症細胞により閉塞していた．
C：内膜の増殖により，血管内腔が閉塞していた．D：内弾性板の断裂を認めた．

表1　入院時検査所見

尿一般：		生化：		免疫：	
尿糖	(−)	TP	6.9 g/dl	抗核抗体	<40倍
蛋白	(−)	ALB	4.2 g/dl	C4	52 mg/dl
潜血	(−)	T.Bil	0.5 mg/dl	C3	153 mg/dl
		AST	15 IU/l	CH50	58.7 mg/dl
赤沈	54 mm/h	ALT	18 IU/l	IgG	874 mg/dl
		ALP	288 IU/l	IgA	162 mg/dl
血算：		LDH	172 IU/l	IgM	91 mg/dl
WBC	10200/μl	CK	79 IU/l	リウマトイド因子	<2 IU/ml
seg	87.0%	Cr	0.87 mg/dl	MPO-ANCA	<1.3 EU
lymph	9.0%	BUN	12.6 mg/dl	PR3-ANCA	<10 EU
mon	3.0%	Na	140 mEq/l	抗カルジオリピン抗体IgG	<4 U/ml
eosin	0.0%	K	4.2 mEq/l	抗カルジオリピンβ2GP I抗体	<1.2 U/ml
RBC	345×10⁴/μl	Cl	105 mEq/l	LAテスト	(−)
Hb	14.5 g/dl	CRP	3.24 mg/dl	HLA type：A33，B44	
Hct	44.4%	血糖	110 mg/dl		
PLT	36.7×10⁴/μl	HbA1c	5.0%		
		フェリチン	60.2 ng/ml		

以後，筋痛が持続したため，3月27日精査加療目的にて入院となった．

入院時現症：身長166 cm，体重63.7 kg．意識清明，体温36.4°C，血圧159/78 mmHg，脈拍71回/分(整)．眼瞼結膜貧血なし，眼球結膜黄染なし．鼻咽頭舌異常なし，口内炎認めず．甲状腺腫大なし，表在リンパ節触知せず．心音，呼吸音は共に異常なし．腹部は平坦・軟，圧痛なし，腫瘤触知せず．四肢に浮腫を認めず．両側下腿に結節性紅斑様皮疹，網状皮斑あり．顔面に毛嚢炎様皮疹を認めた．左前腕から上腕にかけて自発痛を認めたが，把握痛は明らかではなかった．神経学的所見に異常を認めなかった．

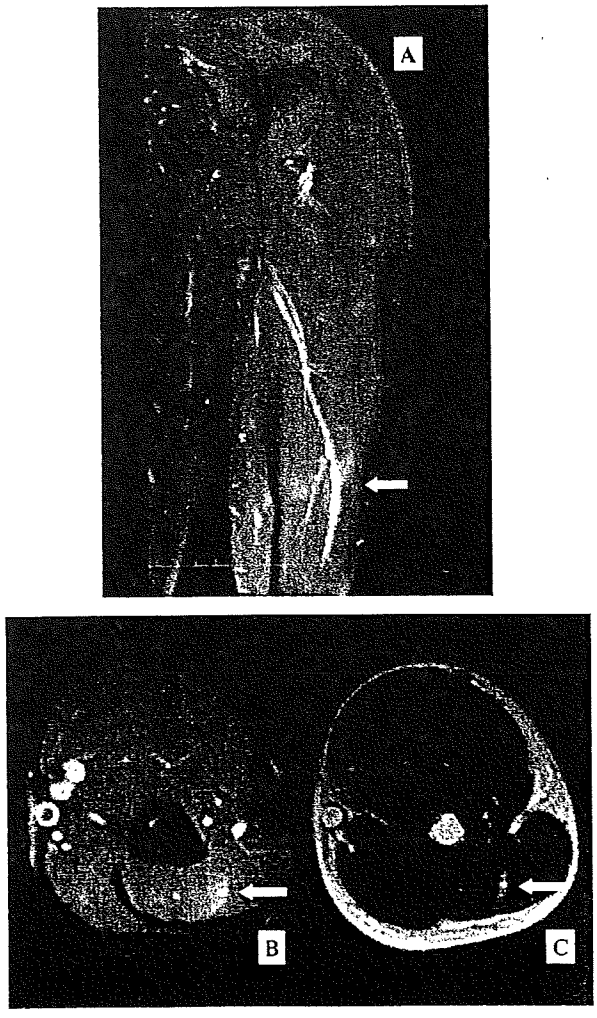

図2　上腕MRI（平成20年4月）

A：冠状断，ガドリニウム造影T1W　B：横断，ガドリニウム造影T1W　C：横断，T2W
左上腕三頭筋内には血管（中側副動脈）に沿った斑状の高信号域が認めた．

入院時検査所見(表1)ではCRP 3.24 mg/dlと上昇を認めたが，筋原性酵素の上昇は認められなかった．また，免疫学的検査では血清補体価の上昇を認めたが，リウマトイド因子，抗核抗体，抗好中球細胞質抗体などの自己抗体は認めなかった．

臨床経過：入院後，全身の精査を行なったが，腎病変などの臓器病変は認めなかった．一方，筋痛に対して左上腕のMRIの検査を施行した．単純MRIでは明瞭ではなかったが，ガドリニウム造影MRIでは血管（中側副動脈）の不整と中側副動脈に沿った斑状の高輝度領域を上腕三頭筋に認めた(図2)．本症例では筋原性酵素の上昇を認めておらず血管炎と二次的な筋の浮腫性変化（または局所の筋炎）と考えられた．4月11日よりPSLを10 mg/日から20 mg/日に，MTXを10 mg/週から12.5 mg/週に増量した．その後，徐々に筋痛は軽快，CRPも陰性化し，5月18日退院となった．

考　　察

本症例は，毛嚢炎，口内炎から当初Behcet病が疑われた．しかし，経過中に眼病変や陰部潰瘍を認めず，HLAの検索ではBehcet病に多いとされるHLA-B51は陰性であった．皮膚生検での壊死性血管炎所見および内臓病変の欠如よりCPANと診断した．また，本症例は多くのPAN症例にみられる体重減少や発熱を経過中に認めず，その点もCPANに矛盾はなかった．一時期，少量のステロイド剤にて経過良好であった．しかし，筋痛の出現，CRPの上昇を認め入院となり，最終的にはPSLおよびMTXの増量にて軽快した．

PANは中・小動脈の壊死性血管炎により，全身の様々な臓器障害をきたす疾患である．臓器障害の頻度は，腎障害は約50%，消化管病変(腸管の壊死や穿孔等)は約40%，多発性単神経炎(しびれ，下垂足)は約65%，脳血管障害(脳出血，脳梗塞)は10～20%にみられる[13)18)]．PANの皮膚病変は約50%に認められ，網状皮斑，皮下結節，皮膚潰瘍，指趾末端の壊疽が主たる病変である．厚生省難治性血管炎分科会(1999年)

の報告によれば，本邦のPAN患者の1年以内の死亡率は約45%と高く，血管炎症候群の中で最も予後不良である[11]．そのためPANの初期治療は，高用量のステロイド剤に加えて，cyclophosphamide (CY) などの免疫抑制薬の併用が推奨されている．

一方，CPANは病変が皮膚に限局し，全身症状が乏しい慢性，再発性の予後良好な疾患とされる[1)3)5)9)14)]．その特徴的な所見は，網状皮斑と疼痛を伴う皮下結節である．初発の皮膚病変は9割以上が下腿でみられる[3]．医学中央雑誌にて過去5年間のCPAN症例を検索したところ，11例の報告があった[4)6)7)10)12)15)16)19)20)]（表2）．その報告例においても，網状皮斑，皮下結節はほぼ全例で認めた．中には難治性の下腿潰瘍や動脈閉塞のため四肢を切断した症例も認め，CPAN症例は必ずしも軽症ではなかった．血液検査では，抗核抗体が42%（5/12例）に陽性であった．

CPANの治療は，軽症のPANに準じステロイド剤単独で開始する[3)5)9)]．ステロイド治療に抵抗性の症例は，MTX[17)]やazathioprine[1)]を追加することがある．表2にまとめたように，CPANの治療にステロイドパルス療法や，CY間欠静注療法，cyclosporinA併用など，強力な免疫抑制療法が施行された症例もあった．特に下腿潰瘍を呈するような重症CPANの治療はPANに準ずる免疫抑制療法が行なわれていた．

以前からMRIは四肢に限局した血管炎患者の評価に有用と報告される[2)]．T1強調画像およびshort tau inversion recovery画像にて骨格筋の病変は，浮腫性変化が高輝度に示される．特に筋生検部位の特定や治療の効果判定に用いられるが，血管病変との関連を評価することは困難である．今回，我々は筋痛の検索において，

表2　本邦における皮膚型結節性多発動脈炎の報告例（過去5年間）

症例	年齢/性別	症状			血液検査		主な治療	文献
		網状皮斑	結節性紅斑（または皮下結節）	その他	ANA	その他		
1	28/M	+	未記載	下腿潰瘍	陰性		PSL 30 mg，CY 100 mg，抗凝固，抗血小板	20
2	54/F	+	+	下腿切断，脛骨動脈閉塞	陽性（軽度）		パルス，IVCY，抗凝固	7
3	50/F	+	+	なし	陽性（320倍）		NSAIDのみ	10
4	53/M	−	+	なし	陽性（40倍）		PSL 30 mg，NSAID	10
5	34/M	−	+	なし	陰性	ASO高値	PSL 60 mg	4
6	22/M	−	+	下肢のしびれ	陰性		パルス，CyA 250 mg	15
7	70/F	+	+	下腿潰瘍	陰性	抗リン脂質抗体陽性	PSL 40 mg，抗凝固	12
8	73/F	+	+	下腿潰瘍	陽性（80倍）	抗リン脂質抗体陽性	PSL 20 mg，抗血小板	12
9	32/F	−	+	下腿潰瘍	陰性	低補体血症	PSL 3 mg	16
10	17/F	+	+	下肢のしびれ	陽性（80倍）		セミパルス，ベタメサゾン3 mg，PG	6
11	66/F	+	未記載	下腿潰瘍，足趾切断	陰性		PSL 60 mg，抗凝固，抗血小板，PG	19
本症例	34/M	+	+	なし	陰性		PSL 20 mg，MTX 12.5 mg，抗凝固	本症例

ガドリニウム造影MRIにて血管炎と二次的な筋の浮腫性変化（または局所の筋炎）を認めた．血管炎と筋病変の関連は，ガドリニウム造影MRIが有用であり，CPANの診断の一助となると考えた．今後の症例の蓄積が期待される．

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ABSTRACT

A case of cutaneous polyarteritis nodosa presenting with characteristic muscle Gadolinium —enhanced MRI findings

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The patient was a 34-year-old male. He visited our hospital for erythema, livedo reticularis, and arthralgia in November 2005. Skin biopsy revealed necrotizing vasculitis and a diagnosis of cutaneous polyarteritis nodosa (CPAN) was made. In March 2008, he was admitted to our hospital for myalgia in the left upper arm.

There was an elevation of CRP but no rise of myogenic enzymes on admission. Autoantibodies, such as rheumatoid factor, antinuclear antibody, and anti-neutrophilic cytoplasm antibody were not detectable. Gadolinium —enhanced MRI of the left upper arm showed an irregularity in the middle collateral artery and patchy areas of high intensity along the middle collateral artery in the triceps brachii muscle. These findings were considered to reflect vasculitis of CPAN and secondary edematous changes of the muscle. The patient was successfully treated with corticosteroids and MTX before being discharged. Gadolinium-enhanced MRI is useful to diagnose muscular lesions associated with vasculitis.

症例報告（推薦論文）
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FDG-PETを契機に大型血管炎の合併を診断し得たリウマチ性多発筋痛症の1例

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A case of polymyalgia rheumatica where a complication of large-vessel vasculitis was diagnosed by FDG-PET

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(Received February 5, 2009)

summary

The patient was a 74-year-old female presenting with abrupt onset of fever and proximal muscle pains. She had been diagnosed with polymyalgia rheumatica (PMR). On physical examination, there was no tenderness or dilatation of the temporal artery and ocular fundi were normal. ^{18}F-FDG-PET revealed accumulation of FDG in the aorta as well as in the bilateral subclavian arteries, which strongly suggested inflammation of the large blood vessels. Magnetic resonance angiography disclosed stenosis of the bilateral subclavian arteries, which was consistent with angitis. This case was considered to have developed PMR at an old age with positive HLA DR4, and to have a complication large-vessel giant cell arteritis (LV-GCA). Administration of prednisolone at a dose of 20 mg/day promptly relieved the fever and the myalgia as well. It is difficult to diagnose GCA in PMR if no tenderness or dilatation of the temporal artery is present. FDG-PET is considered useful, not only for exploration of tumors, but also for evaluation of inflammation of large vessels.

Key words——PMR; LV-GCA; FDG-PET; HLA

抄　録

74歳女性．突然発症の発熱，近位筋痛をきたしリウマチ性多発筋痛症（PMR）と診断された．側頭動脈に圧痛や拡張を認めず，眼底所見も正常であった．18F-FDG-PETを施行したところ，大動脈および両側鎖骨下動脈にFDGの集積を認め大型血管の炎症が強く疑われた．Magnetic resonance angiographyでは，両側鎖骨下動脈の狭窄を認め血管炎の所見に矛盾しなかった．本症例は高齢発症でPMRを合併，さらにHLA DR4陽性で，合併した大型血管炎は大血管型巨細胞性動脈炎（Large-vessel GCA）と考えられた．Prednisolone 20 mg/日の投与を開始し，速やかに解熱．筋痛も改善した．PMRでは側頭動脈の圧痛や拡張等の臨床症状を伴わなければGCAの診断は困難である．FDG-PETは悪性腫瘍の検索だけでなく，PMRに潜在する大型血管炎の評価に有用であると考えられた．

はじめに

リウマチ性多発筋痛症（Polymyalgia rheumatica；PMR）は対称性の近位筋痛をきたす疾患で，65歳以上の高齢者に多く発症する[1]．少量のステロイドに反応し良好な臨床経過をとる症例が多いが，PMRの16～21%[2~4]の症例に巨細胞性動脈炎（Giant cell arteritis；GCA）の合併を認め重篤な経過をとることがある．よって，PMR診断時にはGCAの合併を常に念頭に置く必要がある．

GCAは主に外頸動脈の分枝が侵され，典型例では浅側頭動脈の発赤，拡張，圧痛をきたし側頭動脈炎（Temporal arteritis；TA）とも呼ばれる．また，頭痛や顎跛行，さらに視力の低下などの頭蓋症状を認める[5,6]．一方，GCAの10～15%の症例では，大動脈や鎖骨下動脈などの大型血管が主な標的となる（Large-vessel GCA）[7~9]．これらの症例では鎖骨下動脈や腋下動脈の狭窄をきたし上肢の跛行などの症状を呈する事が多いが，中には典型的な頭蓋症状を

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