Remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) syndrome in Nagano, Japan: Clinical, radiological, and cytokine studies of 13 patients

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Abstract

Objective

Remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) has so far been reported almost exclusively from the USA and Europe. We carried out this study to define the clinical characteristics of this syndrome in Japanese patients.

Methods

Prospectively, we identified 13 Japanese patients with RS_3PE (5 men and 8 women, age 72.7 ± 11.8 years (mean ± SD)) without underlying neoplasm. Their clinical features were summarized, pertinent laboratory data including serum/synovial interleukin-6 (IL-6) concentrations were obtained, and extensive radiologic studies using magnetic resonance imaging and ^{67}gallium-citrate (^{67}Ga) whole body scintigram were performed.

Results

All patients suffered from proximal arthralgia/myalgia in addition to typical distal symptoms of RS_3PE, and all experienced systemic symptoms such as fever, malaise, and weight loss. In laboratory examinations, anemia and elevated inflammatory markers were often remarkable. Magnetic resonance imaging showed severe tenosynovitis of the hands. ^{67}Ga-scintigram revealed radioisotope accumulation in both proximal and distal joints of the extremities. IL-6 activity was markedly elevated both in the serum (mean 82.4 ± 62.1 (SD) pg/ml, normal range 0.157-2.94) and in the synovial fluid (mean 3350 ± 633 (SD) pg/ml).

Conclusion

Compared with cases reported previously from the USA/Europe, Japanese patients with RS_3PE are characterized by more prominent systemic symptoms/signs associated with marked inflammatory responses including elevated IL-6 activity. All patients had proximal as well as distal synovitis which could be demonstrated by ^{67}Ga-scintigram. These clinical features were very similar to those of polymyalgia rheumatica, suggesting that RS_3PE and polymyalgia rheumatica are closely related disorders which may have a common pathogenesis.

Key words

RS3PE, polymyalgia rheumatica, magnetic resonance imaging, gallium scintigram, interleukin-6.

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Introduction

In 1985 and 1990, McCarty and colleagues reported 23 patients with remitting symmetrical synovitis of the extremities associated with marked pitting edema of the dorsum of the hands and feet (1,2). A symmetrical synovitis affecting the flexor tendon sheaths of wrists and hands was considered to be the core clinical finding of this disease entity, accompanied by certain other clinical features including sudden onset, predominance in elderly Caucasian males, negativity for rheumatoid factor (RF), association with human leukocyte antigen (HLA)-B7, and an absence of bone erosions on roentgenogram. The prognosis is universally excellent with a predictable response to low-dose corticosteroid treatment without relapse. They proposed the acronym RS_3PE (remitting seronegative symmetrical synovitis with pitting edema) to define the syndrome because they considered that this clinical constellation is distinct from that of rheumatoid arthritis, polymyalgia rheumatica (PMR), and other seronegative spondyloarthropathies (1, 2).

Since the original description, an increasing number of cases with RS_3PE have been reported from the USA and Europe (3-7), but rarely from Asia (8-10). We report here 13 Japanese patients with RS_3PE. The study aims to clarify the clinical features of RS_3PE in Japan. Moreover, we add some new findings to the scintigraphic and cytokine studies in this syndrome. The results indicate that Japanese patients with RS_3PE have some unique characteristics compared with those in the USA/Europe.

Materials and methods

Patients

Over a 6-year period (1997–2002), we prospectively identified 13 Japanese patients with RS_3PE who were referred to the Third Department of Medicine, Shinshu University School of Medicine, or its affiliated hospitals. All patients showed significant pitting edema in distal extremities accompanied by pain and restriction of movement in affected joints. They all met the clinical characteristics for RS_3PE syndrome, i.e., bilateral pitting edema of the hands, sudden onset of polyarthritis, age > 50 years, and seronegativity for RF (5). These features were also in accordance with those originally described by McCarty *et al.* (1, 2). None of the patients had cardiac or renal diseases based on laboratory, chest roentgenographic, and/or echocardiographic studies. We also excluded patients with Reiter's syndrome, psoriatic arthritis, enteropathic arthropathy, mixed connective tissue disease, relapsing polychondritis, and calcium pyrophosphate dihydrate crystal deposition disease, which may cause puffy hands and/or "sausage-like" fingers resembling those in RS_3PE.

Laboratory tests

All the subjects underwent routine laboratory study. Titers of antinuclear antibody, RF, and HLAwere also obtained. Several markers of inflammation such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) were measured. Synovial fluid was examined in 4 patients. In addition, interleukin-6 (IL-6) activity in the serum from 12 patients and in the synovial fluid from 3 patients was quantified. A commercial chemiluminescent ELISA using a standardized kit was performed to quantify IL-6 (QuantiGlo Human IL-6 Immunoassay, R&D System, Inc., Minneapolis, USA). The normal range of serum IL-6 levels in this measuring system is 0.157–2.94 pg/ml.

Radiological examinations

All patients had roentgenograms taken of the hands and feet. To better elucidate structural alterations in the bone and surrounding soft tissues, magnetic resonance imaging (MRI) of the hands was performed in 12 of 13 patients using a 1.5Tsystem (SIGNA, GE Medical system, Milwaukee; Shinshu University School of Medicine) or a 0.5T system (Magnex α, Shimadzu Medical, Kyoto; National Chusin-Matsumoto Hospital). Pulse sequences included T1-weighted, T2-weighted, and short TI inversion recovery (STIR) scans. Both axial and coronal sections were performed, including gadolinium-en-

Table I. Clinical features of 13 Japanese patients with RS$_3$PE.

Male/Female	5/8
Age (yrs), Median ± SD (range)	72.7 ± 11.8 (55-94)
Duration of illness before diagnosis (weeks) Median ± SD (range)	11.2 ± 9.5 (1-28)
Aching/Joint stiffness (%)	
Shoulder	92.3
Elbow	30.8
Wrist	100
Hip	84.6
Knee	92.3
Ankle	100
Systemic symptoms (%)	
General malaise	100
Loss of appetite	100
Weight loss	92.3
Fever	61.5
Carpal tunnel syndrome (%)	15.4

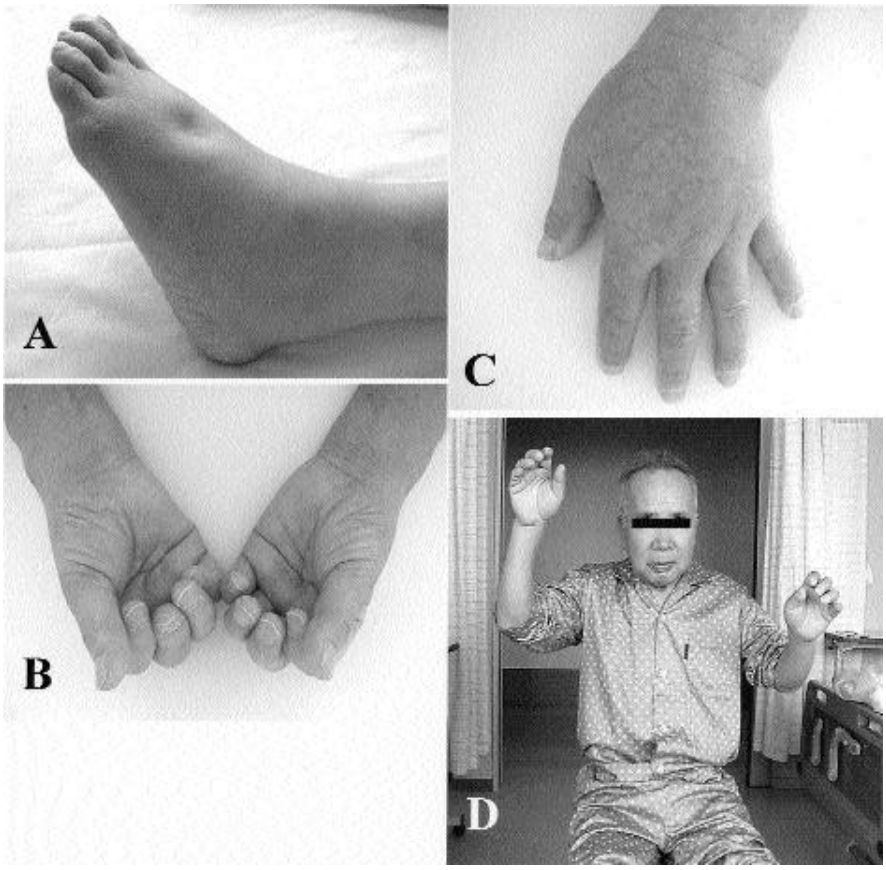

Fig. 1. Symptoms of remitting seronegative symmetrical synovitis with pitting edema observed in our series of Japanese patients.
(**a**) Diffuse swelling and pitting edema on the dorsum of the foot in patient 2.
(**b**) Patient 2 is unable make a fist due to diffuse swelling of the hands and fingers.
(**c**) Diffuse swelling and pitting edema on the dorsum of the hand in patient 4.
(**d**) Patient 4 is asked to raise his hands above his shoulders as high as possible (Japanese 'Banzai').

hanced T1-weighted images. To evaluate the distribution of tenosynovitis, whole body ^{67}gallium-citrate (^{67}Ga)-scintigram study was performed in 10 patients with images obtained 48 hours after injection of 111 MBq of ^{67}Ga. We employed ^{67}Ga in this study because its uptake is directly dependent on the degree of cellular infiltration and the disruption of membrane permeability barriers, features essential for measuring the activity of synovitis (11-13). Twelve of the 13 patients (except patient 1) had MRI, and 10 of the 13 (except patients 1, 6, and 11) underwent ^{67}Ga-scintigram studies before corticosteroid treatment. Four of 13 patients (patients 2-5) underwent follow-up MRI and ^{67}Ga-scintigram studies 8 weeks after the initiation of corticosteroid treatment.

Results

Summary of clinical findings

The clinical findings of the patients are summarized in Table I. The past medical history was unremarkable except for Parkinson's disease in patient 4, and osteoarthritis of the hip joints in patient 6 and of the knee joints in patient 9. The onset of the disease was acute in all patients with no preceding history of infectious disease and/or neoplasm. All patients suffered from arthralgia/myalgia and joint stiffness in both the distal and proximal extremities. Two patients (6 and 10) presented clinical symptoms and signs typical of carpal tunnel syndrome without obvious wasting of thenar muscles. No patient had Raynaud's phenomenon or sclerodactyly. Systemic symptoms/signs were frequent: general malaise, loss of appetite, weight loss, and fever. Fever developed in 8 of the 13 patients (61.5%), and in 6 patients (46.2%) the body temperature rose above 38ºC with frequent spikes.

Representative cases

Patient 2. A 65-year-old Japanese woman was referred to us in August 2000 for evaluation of a 2-month history of progressive weight loss and pain, stiffness and swelling in the bilateral hands and feet, which were unresponsive to non-steroidal anti-inflammatory drugs (NSAIDs). She had also had a persistent fever for 4 weeks, often exceeding 38ºC. On examination, there was obvious swelling with pitting edema over the hands, wrists, and ankles (Fig. 1A). Fine finger movements were severely affected; she could not button herself or use chopsticks because of finger swelling/stiffness. She was unable to make a fist (Fig. 1B). She also suffered from arthralgia/myalgia and stiffness in the proximal joints including the shoulder and hip girdles. The passive range of motion of these joints was not limited. Laboratory data for this patient are shown in Table II (patient 2). No bone destruction was found on X-ray, but ^{67}Ga whole body scintigram revealed symmetrical accumulation of the radioisotope in both the proximal and distal joints. MRI of the hands disclosed prominent tenosynovitis of the flexor and extensor tendon sheaths.

The patient was started on prednisolone at a dose of 30mg daily. All symp-

Table II. Laboratory findings in Japanese patients with RS_3PE before initiation of corticosteroid treatment.

	Pt. 1 94 F	Pt. 2 65 F	Pt. 3 66 F	Pt. 4 65 M	Pt. 5 75 M	Pt. 6 62 F	Pt. 7 83 M	Pt. 8 78 F	Pt. 9 78 F	Pt. 10 61 F	Pt. 11 85 M	Pt. 12 79 F	Pt. 13 55 M
Blood cell count													
WBC (x 10^3/mm^3)	9.5	8.0	13.2	8.8	7.0	5.5	8.0	7.6	6.0	9.5	9.4	7.4	12.3
HB (g/dl)	9.6	9.8	9.1	10.7	11.3	12.1	12.4	8.5	10.4	10.7	13.6	8.4	12.5
Plt (x10^4/mm^3)	55.7	81.4	49.2	34.5	17.1	21.8	33.4	39.1	28.3	55.3	39.5	49.3	30.3
Blood chemistry													
Albumin (g/dl)	2.0	3.4	2.9	3.5	3.0	3.4	3.4	3.0	3.8	3.4	3.7	2.2	3.7
IgG (mg/dl)	923	2043	2132	1308	1511	1135	2160	1752	1358	2145	822	1345	1287
CH50 (U/ml)	46.5	58.8	38.7	39.9	ND	42.9	45.6	72.0	47.4	51.0	52.5	42.4	73.8
Iron (μg/dl)	19	14	20	20	ND	23	10	23	ND	14	ND	15	50
Ferritin (ng/ml)	200	572	609	94	ND	61	74	448	ND	130	ND	140	335
CRP(mg/dl)	16.3	30.1	9.9	7.3	13.7	5.3	3.8	6.5	3.0	7.8	8.2	29.6	19.0
SAA(μg/dl)	ND	ND	105	411	ND	ND	371	363	ND	639	281	768	287
ESR (mm/h)	100	140	118	60	68	57	101	140	106	95	105	126	102
IL-6 (pg/ml)													
Serum	ND	123.0	35.8	61.4	26.5	50.5	48.1	138.0	25.7	110.0	46.6	239.0	84.0
Synovial fluid	ND	3820	ND	3600	2630	ND	ND	ND	ND	ND	ND	ND	ND

F: female; M: male; WBC: total white blood cell count; HB: hemoglobin; Plt: platelet count; IgG: immunoglobulin G; CRP: C-reactive protein; SAA: serum amyloid A; ESR: erythrocyte sedimentation rate; IL-6: interleukin-6; ND: not done.

toms resolved within a week and laboratory abnormalities normalized within 3 weeks. After 4 weeks, prednisolone was tapered. MRI of the hands and ^{67}Ga-scintigram 8 weeks after corticosteroid treatment revealed obvious improvement of synovitis. In January 2001, she developed mild ankle arthralgia without edema when she was on prednisolone 5mg daily. ESR was normal but CRP was slightly elevated (1.2 mg/dl). This flare-up subsided promptly with the addition of 10mg of prednisolone. The corticosteroid was gradually tapered again to a maintenance dose of 2.5mg daily without further recurrence. In August 2002, prednisolone was stopped. She has remained entirely asymptomatic up until March 2003. No residual contractures or deformities of the joints were observed.

Patient 4. A 65-year-old Japanese man, the owner of a *soba* noodle restaurant, with Parkinson's disease (severity score 3 using Yahr's classification) presented with a 2-week history of pain, stiffness, and swelling of his hands and feet. He could not take the cap off a bottle, and had great trouble in making *soba* noodles. He complained of general malaise and fatigue. Low-grade fever was noted. The physical examination revealed pitting edema over the dorsum of the hands and feet (Fig. 1C). He complained of arthralgia and/or myalgia of the shoulder and hip girdles. The range of motion of the shoulders was limited because of severe pain (Fig. 1D). The laboratory data are shown in Table II (patient 4). Imaging studies of the hands revealed no bone erosion on X-ray, but MRI showed signs of tenosynovitis. Symmetrical radioisotope accumulation in the shoulders, hips, wrists, and metacarpophalangeal joints was evident on scintigram. He was started on prednisolone at a dose of 20 mg daily, and the symptoms resolved within one week. The corticosteroid was gradually tapered off over 8 months and he has remained symptom-free for the last 28 months.

Laboratory findings

The results of routine laboratory tests are shown in Table II. Leukocytosis was found in 2 patients (15.4%), while more than half of the patients showed thrombocytosis. Mild to moderate anemia of the normocytic-normochromic type was frequent (84.6%, 11/13), associated with a low level of serum iron (90%, 9/10) and an elevated serum ferritin concentration (70%, 7/10). Inflammatory markers were elevated in all patients in whom they were measured: CRP 12.3 ± 9.1mg/dl (n = 13), normal < 0.5; SAA 403.1 ± 210.1 μg/ml (n = 8), normal < 8.0; ESR 100.6 ± 30.0mm/hr (n = 13), (mean ± SD). All patients were negative for antinuclear antibody and also for RF (by definition). Activity of IL-6 in the serum was markedly elevated in all the patients examined (mean 82.4 ± 62.1 (SD) pg/ml, reference range 0.157 – 2.94). HLA typing was performed in 10 patients: two (patients 6 and 9) were HLA-B7 positive; one (patient 8) was HLA-B27 positive; four (patients 4, 5, 7, and 8) were HLA-DR4 positive. Synovial fluids were examined in four patients (patients 1, 2, 4, and 5). They were mildly turbid and revealed mononuclear cell-dominant leukocytosis without any crystals. Cultures of synovial fluids were sterile. Activity of IL-6 in the synovial fluid was consistently higher than in the serum (mean 3350 ± 633 (SD) pg/ml).

Radiological findings

Roentgenogram. X-rays of hands and feet in all 13 patients showed no abnormality of the bones and joints, except for Heberden's nodes seen in patient 1.

MRI. The MRI study performed in 12 patients revealed prominent tenosynovitis manifested by the presence of

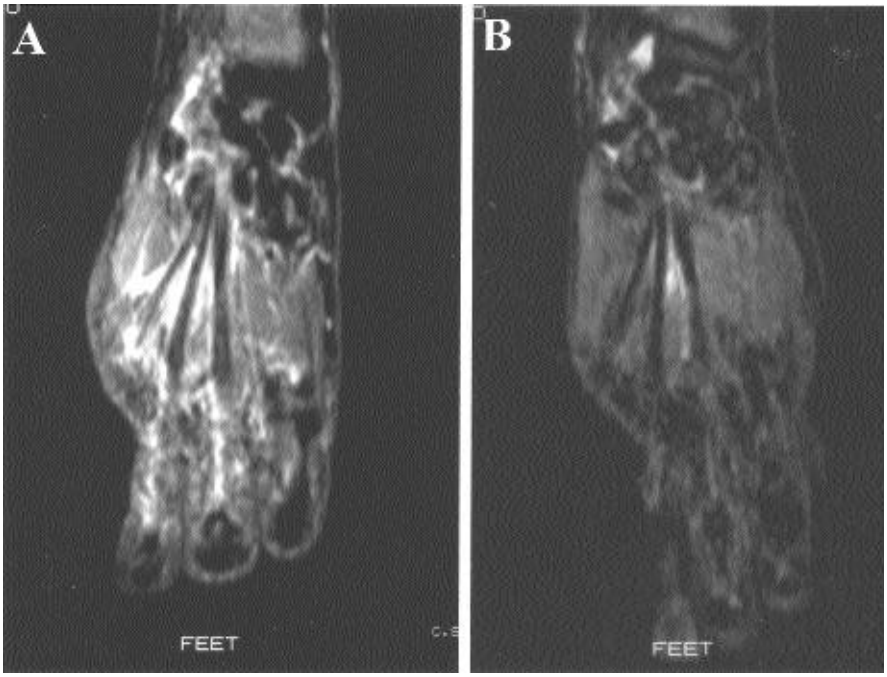

Fig. 2. MRI (STIR sequences) of the hand in patient 3 before (**a**) and after treatment (**b**).
(**a**) Before corticosteroid treatment. Coronal section of the right hand shows marked edematous/inflammatory changes around the flexor tendon sheaths. An increased signal intensity is also observed within subcutaneal tissues and intrinsic hand muscles.
(**b**) 8 weeks after corticosteroid treatment. Coronal section of the right hand shows reduced inflammatory changes.

Table III. Semiquantitative evaluation of joint involvement by ^{67}Ga-citrate scintigram.

	Proximal joints				Distal joints			
	Upper limbs		Lower limbs		Upper limbs		Lower limbs	
	Shoulder	Elbow	Hip	Knee	Wrist	MCP*	Ankle	MTP**
Pt.2	+++	+	+++	+	++	+	+	+
Pt.3	+++	+	++	+	++	++	+	+
Pt.4	+	-	+	-	+	+	-	-
Pt.5	+	-	+	-	++	+	+	+
Pt.7	+++	+	+++	+++	++	++	++	+
Pt.8	++	-	++	+	+	+	+	+
Pt.9	+	-	+	-	+	-	-	-
Pt.10	++	+	++	++	++	+	+	-
Pt.12	++	-	++	+	+	-	+	-
Pt.13	++	+	++	+	++	+	+	+

* Metacarpophalangeal joints; ** metatarsophalangeal joints
Semiquantitative assessment of the degree of radiopharmaceutical accumulation in the joints, based on a 4-grade scale: (-) within normal limits; (+) slight to mild accumulation was seen, but less than in the liver; (++) moderate accumulation was observed, almost equal to that in the liver; (+++) marked accumulation was observed, more than in the liver.

fluid in the tenosynovial sheaths of the hands. The extensor and flexor tendon sheaths of the hands from wrist to midpalm were most severely affected in all the patients examined. Increased signal intensity on T2-weighted/STIR sequences spread over the soft tissues and intrinsic hand muscles surrounding flexor tendon sheaths of the hands (Fig. 2A). Gadolinium-enhanced MRI sequences revealed apparent enhancement of tendon sheaths. Four patients (patients 2-5) underwent follow-up MRI study after corticosteroid treatment: MRI of the hands obtained 8 weeks after therapy revealed reduction of the inflammatory changes around the tendon sheaths (Fig. 2B).

^{67}Ga-Scintigram. ^{67}Ga whole body scans obtained from 10 patients revealed radiopharmaceutical accumulation in the wrists, ankles, and metacarpophalangeal and metatarsophalangeal joints symmetrically. Overall, uptake of the radioisotope was also evident in the proximal joints (Fig. 3A). Uptake was semiquantitatively evaluated and is summarized in Table III. Accumulation of ^{67}Ga in the proximal large joints (shoulders and hips) was more than equal to that in the distal joints in all patients except patient 5. In addition, 4 patients (patients 2-5) who underwent follow-up ^{67}Ga-scintigram 8 weeks after corticosteroid treatment showed a marked decrement of radioisotope accumulation in both proximal and distal joints (Fig. 3B).

Outcome

Various NSAIDs had been prescribed to patients 1-3, 5, 6 and 10-13 with little benefit. After being diagnosed with RS$_3$PE, all patients received oral corticosteroid treatment. Oral prednisolone 20-30 mg daily resulted in prompt relief of the pain within 24 to 72 hours, followed by a complete disappearance of signs and symptoms within 2 to 3 weeks. Laboratory abnormalities also improved promptly: elevated CRP and SAAvalues were normalized within 1-2 weeks, ESR within 2–3 weeks, and anemia, thrombocytosis, and hypoalbuminemia were almost resolved within 3–5 weeks. Prednisolone was gradually tapered to 5–2.5 mg daily without recurrence, except in three patients (patients 1, 2, and 6) who developed mild wrist and/or ankle arthralgia with mild elevation of CRP (up to 2 mg/dl) at a dose of 5 mg daily oral prednisolone. The flare-up of symptoms subsided promptly on the addition of 5–10 mg of oral prednisolone. The follow-up period was from 9 to 31 months (mean 20.4 months). During the period, corticosteroid treatment could be stopped in three patients: patients 2, 4, and 5 were able to interrupt prednisolone 23, 8, and 15 months after the initiation of the treatment, respectively. No patient developed articular erosions or met the

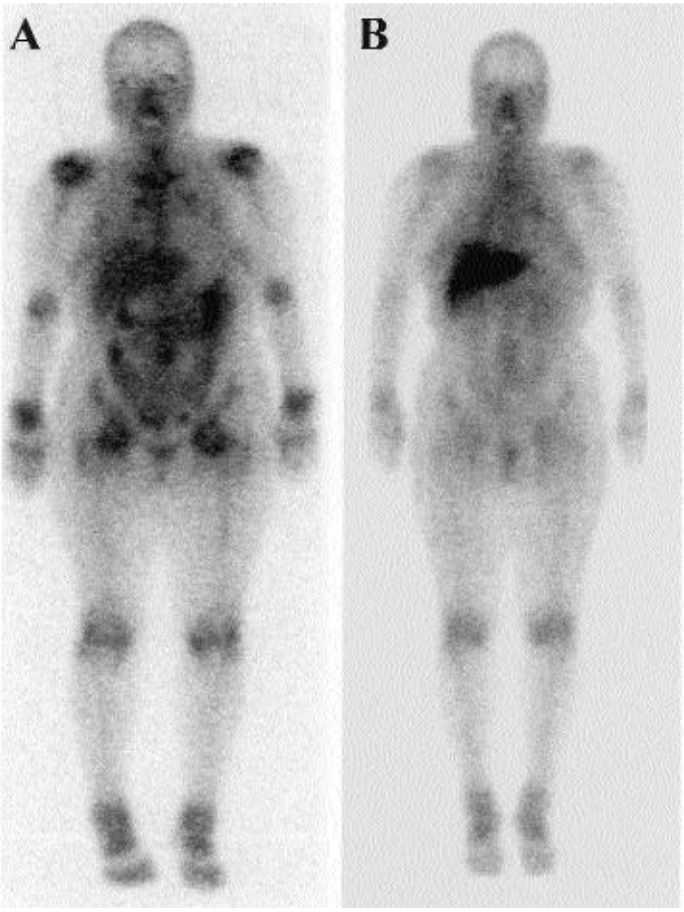

Fig. 3. ^{67}Ga-scintigram in patient 2 before (**a**) and after the treatment (**b**).
(**a**) Pre-treatment whole body scan revealed an increased radioisotope uptake, evident in both proximal and distal limb joints.
(**b**) Whole body scan taken 8 weeks after corticosteroid treatment. A reduced radioisotope uptake in the joints is clearly shown, whereas uptake in the liver is normalized.

Table IV. Comparison of clinical characteristics of RS_3PE between USA/Europe and Japan.

	USA/Europe				Japan	
	Refs. 1, 2 (n = 23)	Ref. 4 (n = 24)	Ref. 5 (n = 27)	Ref. 6 (n = 23)	Refs. 8-10 (n = 5)	Our study (n = 13)
Age (yr)*	68.9 ± 8.1	71.4 ± 7.7	71.7 ± 8.7	74.0 ± 9.0	61.8 ± 10.7	72.7 ± 11.8
M/F ratio	2.3	3.8	2.0	1.1	0.7	0.6
Fever (%)	ND	ND	3.7	9.0	60.0	61.5
HLA-B7 (%)	61.9	22.2	ND	15.0	0	20.0
HB (g/dl)*	12.5 ± 2.7	ND	ND	ND	10.3 ± 0.6	10.7 ± 1.6
CRP(mg/dl)*	ND	ND	ND	6.3 ± 5.0	12.5 ± 7.9	12.3 ± 9.1
ESR (mm/h)*	51.3 ± 29.6	66.0 ± 31.0	50.9 ± 32.3	74.0 ± 30.0	87.8 ± 26.7	100.6 ± 30.0

* mean ± SD
M: male; F: female; HLA: human leukocyte antigen; HB: hemoglobin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ND: not described.

American Rheumatism Association 1987 modified criteria for the diagnosis of rheumatoid arthritis (14) over the follow-up. No malignancy or other connective tissue diseases developed in any of the 13 patients.

Discussion

All the patients in our series could be diagnosed as having RS_3PE because they revealed typical clinical characteristics of RS_3PE as described in previous reports (1,2,5). Recently, an increasing number of patients with RS_3PE accompanied by solid or blood malignancies (so-called "paraneoplastic" RS_3PE) have been reported (15, 16). However, none of our patients had neoplasms at the time of presentation, or developed them during the follow-up of 9 to 31 months. Therefore, our patients could be regarded as "pure" RS_3PE (15, 16). RS_3PE is considered to be a relatively common syndrome in the USA/Europe (1, 2, 5, 6), but has so far been rarely reported in other countries. To our knowledge, only five cases of "pure" RS_3PE were previously reported from Japan (Table IV) (8-10).

Our patients and those reported in the literature are summarized comparatively in Table IV. It is noteworthy that several clinical features common to RS_3PE cases reported from the USA/Europe were not recognized in Japanese patients with RS_3PE, i.e., male predominance (4:1 to 2:1) (1, 2, 4-7), high incidence of the HLA-B7 subtype (approximately 50%) (1, 2), little deterioration in general health status (3, 6, 15), and absence of greatly elevated ESR (17). In contrast, systemic symptoms/signs including malaise, fever, weight loss, and laboratory abnormalities, i.e., severity of anemia, ESR, and activity of acute phase reactants, were more prominent in Japanese patients as compared with those reported from the USA/Europe (1,2,4-6). The reasons for the differences are unclear. They may reflect a racial difference with different genetic backgrounds between Caucasians and Japanese, or be the result of a bias due to the limited number of Japanese patients studied. In this regard, it is interesting to note that a previous comprehensive study of Japanese patients with PMR revealed that fever, anemia, and greatly elevated ESR were more commonly found in Japanese patients than in European patients (18), suggesting that prominent systemic symptoms/signs are common clinical features of PMR and RS_3PE in Japanese patients.

In the present study, we measured concentrations of IL-6 in the serum and synovial fluid for the first time in patients with RS_3PE, and found a striking elevation of IL-6 activity in both serum and

synovial fluid. In PMR, increased serum/plasma IL-6 activity has been reported as a characteristic finding in the disease, which may be responsible for certain clinical symptoms secondary to the induction of acute phase reactant activity (19,20). The level of IL-6 may even define the responsiveness to treatment (21). Furthermore, CD14-expressing peripheral blood monocytes have been proved to be the exclusive source of circulating IL-6 in patients with PMR (20). In our patients with RS_3PE we found that the level of IL-6 was consistently much higher in the synovial fluid than in the serum (n = 4). Since the synovium is considered to be a primary target of this disease (22,23), it is possible that locally produced IL-6 in the synovium may dissipate into circulation, resulting in the generalized symptoms of RS_3PE.

Ever since it was first described, there has been considerable controversy regarding the nosological identity of RS_3PE, because RS_3PE and PMR share certain demographic, clinical, and MRI findings (4-6, 22-27). The clinical features in the Japanese patients with RS_3PE that we and others have studied, i.e., proximal arthralgia/myalgia and systemic symptoms, overlap considerably with those of PMR except for the striking distal extremity symptoms. Up to the present, distal extremity symptoms have been regarded as cardinal features of RS_3PE. However, a review of the literature revealed that a small number of RS_3PE patients with proximal symptoms have been reported (4, 5). In PMR, in addition to MRI/sonographic evidence of inflammation of the periarticular synovial structure in the proximal extremities (28-31), previous radioisotope studies documented not only proximal but also distal joint involvement, although proximal joints tended to be more frequently affected (32,33). Furthermore, recent MRI studies have confirmed that the tenosynovitis of the hands and feet reflects the broader inflammatory process of PMR, and that the hand extensor tendon apparatus is the anatomical structure most frequently involved in PMR (23, 26, 28), similar to RS_3PE (6). Additionally, our scintigraphic study revealed obvious proximal as well as distal joint accumulation in all the RS_3PE patients examined. This finding receives some support from previous radioisotope studies on RS_3PE including ^{67}Ga-scintigram (9) and ^{99m}technetium diphosphonate scintigram (1), in which inflammation of the proximal joints has been clearly demonstrated. Taken together our clinical, radiological, and cytokine studies support the view that PMR and RS_3PE may form part of the clinical spectrum of the same disease. We consider that typical PMR and RS_3PE represent both ends of the spectrum of the same disease, the former being the proximal-dominant form, and the latter the distal-dominant form.

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